Association between use of amiodarone for non-valvular atrial fibrillation and patient survival: from the prospective China Atrial Fibrillation Registry

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Abstract

Background: *Post hoc* analysis of the landmark atrial fibrillation follow-up investigation of rhythm management trial revealed that amiodarone was associated with higher risks of mortality, intensive care unit admission, and non-cardiovascular death. We aim to evaluate the association between amiodarone use and patient survival under updated medical mode and level using data from the China Atrial Fibrillation (China-AF) Registry study.

Methods: Clinical data of 8161 non-valvular atrial fibrillation (NVAF) patients who were antiarrhythmic drug (AAD)-naive before enrollment into the China-AF Registry, recruited between August 2011 and February 2017, were collected. The primary outcome was all-cause mortality. A Cox proportional hazard regression model was used to evaluate the association between amiodarone use and the outcome. We also calculated the rate of sinus rhythm maintenance at the penultimate follow-up.

Results: Compared with 6167 patients of non-AAD group, 689 patients of the amiodarone group were younger (mean age 65.6 *vs.* 68.6 years), more frequently completed high school education, had fewer comorbidities such as chronic heart failure, prior bleeding, and stroke, and were more likely to be treated in tertiary hospitals while less hospitalization. The proportion of persistent AF was much lower among users of amiodarone, who were also less likely to be taking oral anticoagulants. The patients in the amiodarone group had a statistically insignificant lower incidence of all-cause mortality (2.44 *vs.* 3.91 per 100 person-years) over a mean follow-up duration of 300.6 ± 77.5 days. After adjusting for potential confounders, amiodarone use was not significantly associated with a lower risk of all-cause mortality (adjusted hazard ratio, 0.79; 95% confidence interval, 0.42–1.49). Sub-group analysis revealed the consistent results. The rate of sinus rhythm maintenance at the penultimate follow-up in the amiodarone group was significantly higher than in the non-AAD group.

Conclusions: Our study indicated that amiodarone use was not significantly associated with a lower risk of 1-year all-cause mortality compared with a non-AAD strategy in "real-world" patients with NVAF.

Keywords: Atrial fibrillation; Amiodarone; All-cause mortality

Introduction

Atrial fibrillation (AF) impairs patients' quality of life and substantially increases their risks of morbidity and mortality. It also imposes great challenges to health care systems worldwide.[1-3] Rate-control and rhythm-control therapies combined with antithrombotic therapy have been the primary strategies for AF management since the early 1990s. Antiarrhythmic drugs (AADs) are traditionally regarded as the cornerstone for restoration and maintenance of sinus rhythm.[4] Amiodarone is one of the most widely used AADs.[4,5]

Several clinical trials[6-10] and observational studies[11-14] comparing the effects of rhythm-control and rate-control strategies on the prognosis of patients with AF have been published in the last two decades, and their results have promoted updates to the guidelines of AF management[5,15,16] and subsequent changes in clinicians' treatment patterns.[17,18] Amiodarone was one of the most frequently used AADs in these studies. However, its association with patient survival in comparison with rate-control medications has never been independently investigated; only a *post-hoc* analysis of the landmark atrial fibrillation follow-up investigation of rhythm management (AFFIRM)[8] trial revealed that amiodarone was associated with higher

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risks of mortality, intensive care unit admission, and non-cardiovascular death.[19]

Therefore, the present study was performed to evaluate the association between amiodarone use and patient survival under current medical mode and level using data from the China Atrial Fibrillation (China-AF) Registry study.

Methods

Study population

The rationale and design of the China-AF Registry study have been described previously.[20,21] In brief, the China-AF Registry study was a prospective, multicenter, hospital-based registry study. In total, 20,666 patients were enrolled from 31 tertiary and secondary hospitals in Beijing from August 2011 to February 2017. The present study was based on data from the China-AF Registry study (No. ChiCTR–OCH–13003729; http://www.chictr.org.cn/showproj.aspx?proj = 5831). The Human Research Ethics Committee at Beijing Anzhen Hospital approved the present study, and the ethics review boards at individual participating hospitals approved their participation. Written informed consent was obtained from each patient.

Patients with non-valvular atrial fibrillation (NVAF) were identified from the China-AF Registry study database. For the present analyses, we excluded patients aged <18 years, those with valvular AF, those with <6 months of follow-up or who lacked follow-up data, those who had used AADs before registry enrollment, and those who underwent catheter ablation or surgical ablation during the index hospitalization. Patients who underwent ablation therapy during follow-up were censored at the time of ablation; however, we excluded patients with a <6-month duration between their registry enrollment and ablation.

Patients who received amiodarone upon registry enrollment and during follow-up were classified into the amiodarone group and were censored at the time of discontinuation during the follow-up period according to the "as treated" definition of exposure. Patients who used no class I or III AADs were classified into the non-AAD group [Figure 1], and they were censored 1 year after registry enrollment.

Data collection

The following data were collected upon patient enrollment: socio-demographic characteristics (age, sex, education status, and medical insurance coverage); medical history, including established coronary artery disease (CAD), diabetes mellitus, hypertension, hyperlipidemia, chronic heart failure (CHF), major bleeding, previous stroke/transient ischemic attack (TIA)/peripheral thromboembolism (TE), liver function, renal function (presented as estimated glomerular filtration rate [eGFR]), AF type (new-onset, paroxysmal, or persistent), and time of AF diagnosis; medication history; and patient treatment site. The patients were followed up at 3, 6 months, and every 6 months thereafter by trained staff at the outpatient clinics or through telephone interviews. Data regarding the patients' heart rhythm, medical therapies, and all-cause death were recorded. Patients were considered lost to follow-up if they refused to be followed up or we were unable to contact them by three telephone calls a day for 5 working days.

Established CAD was defined as having any history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting. Abnormal liver function was defined as having serum level of aspartate aminotransferase or alanine aminotransferase >120 U/L and total bilirubin >34.2 μmol/L. The eGFR was calculated using the abbreviated equation from the Modification of Diet in Renal Disease study.[22]

Study outcome

The primary outcome of the study was all-cause mortality. Death that occurred before amiodarone use was not considered an event of interest. We also evaluated the rate of sinus rhythm maintenance at the penultimate follow-up.

Statistical analysis

Descriptive data are presented as mean ± standard deviation for continuous data and as number (percentage) for categorical data. Baseline characteristics and clinical outcomes were compared between the amiodarone group and non-AAD group using Student's *t* test (for continuous variables) or the Chi-square test (for categorical variables). We used multiple imputation to fill in the missing values.

The rate of overall death during follow-up was depicted in Kaplan-Meier curves and compared using the log-rank test. A Cox proportional hazard regression model was used to evaluate the hazard ratios and their 95% confidence intervals of amiodarone use with the outcome. Before modeling, we removed the survival person-time between registry entry and the first prescription of amiodarone during follow-up to minimize immortal time bias.[23]

The multivariate model was adjusted for potential confounders including baseline age, sex, education status (high school completion), health insurance coverage (partial or complete health insurance coverage), body mass index, current smoking and current drinking, history of established CAD, diabetes mellitus, hypertension, hyperlipidemia, CHF, previous bleeding, stroke/TIA/TE, abnormal liver function, eGFR of <60 mL·min^{-1}·1.73 m^{-2}, AF type (persistent AF), time since diagnosis of AF (≥12 months), and hospital level (tertiary hospital). We also included oral anticoagulant (OAC) use and hospitalization history at the penultimate follow-up as time-dependent covariates in the multivariable models. A subgroup analysis was conducted to explore the differential effects of amiodarone use on the risk of overall mortality by age (<75 *vs.* ≥75 years), sex, previous CAD, CHF, AF type (paroxysmal *vs.* persistent), and time since AF diagnosis (<12 *vs.* ≥12 months). The rate of sinus rhythm maintenance was evaluated by the Chi-square test.

All statistical tests were two-tailed, and a *P* value of <0.05 was considered statistically significant. All analyses were

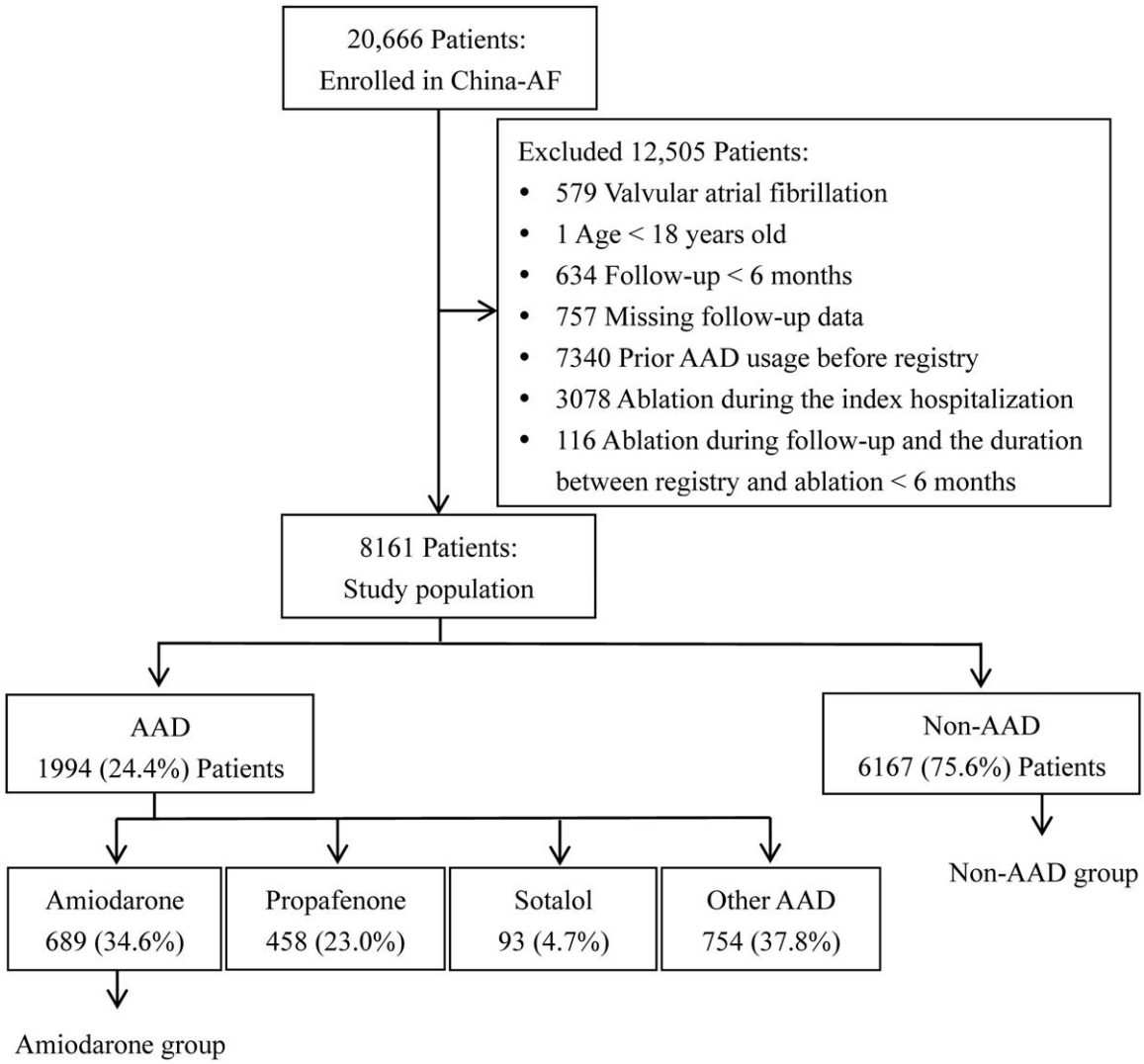

Figure 1: Patient flowchart. This figure shows how eligible patients were included and grouped by amiodarone use. AAD: Antiarrhythmic drug; China-AF: China Atrial Fibrillation Registry.

conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

Among 8161 patients with NVAF included in the present study, 1994 (24.4%) received either class I or III AAD therapy. Of these 1994 patients, 689 (34.6%) received amiodarone. A total of 6167 (75.6%) patients had no history of taking any AADs. A patient flowchart is shown in Figure 1.

Baseline characteristics

Table 1 shows that compared with the non-AAD group, the patients in the amiodarone group were younger (mean age, 65.6 *vs.* 68.6 years); more frequently completed high school education; had fewer comorbidities such as CHF, prior bleeding, and stroke with the exception of previous CAD, diabetes mellitus, and hypertension; were more likely be treated in tertiary hospitals; and were more likely to have undergone a higher number of hospitalizations. The proportion of new-onset and paroxysmal AF was much higher among users of amiodarone, who were also less likely to be taking OACs. The use of β blockers was comparable between the amiodarone and non-AAD groups, and the use of digoxin was 8.9% and 14.1% in each group, respectively [Table 1].

All-cause mortality

The event-free survival curves are shown in Figure 2. Compared with the non-AAD group, the patients in the amiodarone group had a lower incidence of all-cause mortality (2.44 *vs.* 3.91 per 100 person-years) during a mean follow-up duration of 300.6 ± 77.5 days; however, the difference was not statistically significant.

Multiple regression analysis with adjustment for potential baseline confounders and time-dependent covariates including OAC use and treatment site at the penultimate

Table 1: Baseline patient characteristics by amiodarone use from the prospective China Atrial Fibrillation (China-AF) Registry.

Patient characteristics*	Overall (*N* = 6856)	Amiodarone group (*n* = 689)	Non-AAD group (*n* = 6167)	Statistical values	*P*
Demographics					
Age (years)	68.3 ± 11.9	65.6 ± 11.8	68.6 ± 11.9	6.19*	<0.001
Male	4031 (58.8)	406 (58.9)	3625 (58.8)	0.01†	0.941
High school completion	1655 (26.9)	197 (32.6)	1458 (26.3)	11.16†	<0.001
Partial or complete health insurance coverage	6307 (92.1)	622 (90.4)	5685 (92.2)	2.86†	0.091
BMI (kg/m^2)	25.4 ± 3.7	25.7 ± 3.8	25.4 ± 3.7	−2.01*	0.045
Current smoking	1080 (15.9)	123 (17.9)	957 (15.7)	2.34†	0.126
Current drinking	1289 (19.0)	150 (21.9)	1139 (18.7)	4.10†	0.043
Medical history					
Established CAD	1157 (16.9)	131 (19.0)	1026 (16.7)	2.46†	0.116
DM	1954 (28.5)	195 (28.3)	1759 (28.5)	0.02†	0.895
Hypertension	4814 (70.3)	488 (70.8)	4326 (70.2)	0.12†	0.730
Hyperlipidemia	3035 (44.3)	335 (48.6)	2700 (43.8)	5.76†	0.016
CHF	1730 (25.2)	128 (18.6)	1602 (26.0)	18.04†	<0.001
Previous bleeding	364 (5.3)	23 (3.3)	341 (5.5)	5.94†	0.015
Previous stroke/TIA/TE	1412 (20.6)	104 (15.1)	1308 (21.2)	14.24†	<0.001
Abnormal liver function‡	236 (4.8)	26 (4.8)	210 (4.8)	0.01†	0.928
OAC usage	1484 (21.7)	112 (16.3)	1372 (22.3)	13.21†	<0.001
eGFR ($mL{\cdot}min^{-1}{\cdot}1.73{\cdot}m^{-2}$§)	102.3 ± 32.9	104.9 ± 30.5	102.0 ± 33.2	−2.03*	0.043
AF type					
New-onset AF	799 (11.7)	118 (17.1)	681 (11.1)	22.05†	<0.001
Paroxysmal AF	2773 (40.5)	383 (55.6)	2390 (38.8)	72.08†	<0.001
Persistent AF	3270 (47.8)	188 (27.3)	3082 (50.1)	129.13†	<0.001
Diagnosis of AF ≥12 months	3596 (52.5)	320 (46.4)	3276 (53.1)	11.08†	<0.001
Rate-lowering drugs					
β blockers	3910 (57.0)	384 (55.7)	3526 (57.2)	0.53†	0.468
Non-dihydropyridine calcium-channel antagonists	456 (6.7)	42 (6.1)	414 (6.7)	0.38†	0.537
Digoxin	932 (13.6)	61 (8.9)	871 (14.1)	14.65†	<0.001
Tertiary hospital admission	5304 (77.4)	555 (80.6)	4749 (77.0)	4.45†	0.035
Inpatients	2,718 (39.7)	337 (48.9)	2381 (38.7)	27.25†	<0.001
Follow-up duration (days)	300.6 ± 77.5	239.1 ± 108.0	340.8 ± 65.8	24.24*	<0.001

Data are presented as mean ± SD or *n* (%). *t values. †χ^2 values. ‡Liver function was obtained in 4955 patients (537 in the amiodarone group and 4418 in the non-AAD group). Abnormal liver function was defined as a serum aspartate aminotransferase or alanine aminotransferase concentration of >120 U/L and total bilirubin concentration of >34.2 μmol/L. §eGFR was obtained in 4918 patients (529 in the amiodarone group and 4389 in the non-AAD group). eGFR ($mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$) = 186 × (SCr [μmol/L] × 0.0113)$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female), where SCr is the serum creatinine concentration. AAD: Antiarrhythmic drug; AF: Atrial fibrillation; BMI: Body mass index; CAD: Coronary artery disease; CHF: Chronic heart failure; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; OAC: Oral anticoagulants; SD: Standard deviation; TE: Thromboembolism; TIA: Transient ischemic attack

follow-up revealed that age, CHF, stroke/TIA/TE, abnormal liver function, eGFR of <60 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$, and hospitalization at the penultimate follow-up were independent risk factors for all-cause mortality. Body mass index, hyperlipidemia, tertiary hospital, and OAC use at the penultimate follow-up were independent markers of lower overall death. Compared with the non-AAD group, the association between amiodarone use and all-cause mortality was not statistically significant (adjusted hazard ratio, 0.79; 95% confidence interval, 0.42–1.49) [Table 2].

The lack of a significant association between amiodarone use and all-cause mortality was consistent in different subgroups defined by age (<75 *vs.* ≥75 years), sex, previous CAD, CHF, AF type (paroxysmal *vs.* persistent), and time since AF diagnosis (<12 *vs.* ≥12 months) [Figure 3].

The prevalence of sinus rhythm in the overall study population was 41.7% at the penultimate follow-up and was higher in the amiodarone group than in the non-AAD group (55.7% *vs.* 40.1%, $P < 0.001$) [Table 3].

Discussion

Our previous study[24] revealed that overall AAD use was associated with a lower risk of 1-year all-cause mortality than was a non-AAD strategy in patients with NVAF under current medical mode and level. In the present study, we further investigated the association between amiodarone use and overall death of patients with NVAF and found no statistical significance.

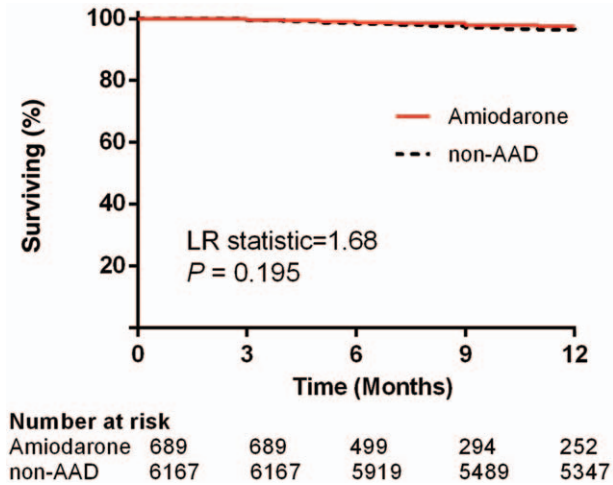

Figure 2: Kaplan-Meier curves for 1-year all-cause mortality. This figure shows Kaplan-Meier curves for all-cause mortality among patients with non-valvular AF enrolled in the China-AF Registry from 2008 to 2015 by amiodarone use. AAD: Antiarrhythmic drug; AF: Atrial fibrillation; LR: Log-rank.

Profile of AAD use

With the update of AF management guidelines,[5,15] clinicians are seeking more effective and safer medications and treatment strategies for patients with NVAF. As for patients with left ventricular hypertrophy, CHF, and established CAD, amiodarone is recommended before sotalol and propafenone, which might be associated with a higher mortality rate.[18,25,26]

In the AFFIRM trial[8] and a retrospective study of AAD use in England,[17] amiodarone and sotalol constituted up to 70% to 85% of the overall AADs. In the present study, amiodarone and propafenone were the two most commonly used AADs, amounting to 57.5% of AADs. However, the proportion of sotalol use was only 4.7%, which was quite different from that in Western countries. Moreover, 754 (37.8%) patients in this observational study received other antiarrhythmic agents (such as moricizine), switched between different AADs, or received a combination of AADs.

Table 2: Association between amiodarone use and all-cause mortality at 1 year.

	Unadjusted		Adjusted	
Characteristics	**HR (95% CI)**	***P* value**	**HR (95% CI)***	***P* value**
Age (years)	1.08 (1.06–1.09)	<0.001	1.04 (1.03–1.06)	<0.001
Men	1.04 (0.81–1.35)	0.745	1.29 (0.96–1.72)	0.088
Completed high school	0.62 (0.44–0.88)	0.008	0.83 (0.53–1.3)	0.399
Partially or complete health insurance coverage	1.10 (0.67–1.8)	0.704	0.90 (0.55–1.49)	0.688
BMI (kg/m^2)	0.87 (0.84–0.91)	<0.001	0.92 (0.89–0.96)	<0.001
Current smoking	1.04 (0.73–1.48)	0.822	1.44 (0.95–2.18)	0.083
Current drinking	0.60 (0.41–0.9)	0.012	0.77 (0.49–1.21)	0.261
Established CAD†	1.69 (1.26–2.27)	<0.001	1.21 (0.89–1.63)	0.229
DM	1.42 (1.09–1.85)	0.009	1.10 (0.84–1.46)	0.482
Hypertension	1.15 (0.86–1.53)	0.346	0.74 (0.55–1.02)	0.062
Hyperlipidemia	0.68 (0.52–0.89)	0.005	0.70 (0.53–0.92)	0.011
CHF	4.27 (3.29–5.53)	<0.001	1.85 (1.38–2.47)	<0.001
Previous bleeding	1.65 (1.04–2.61)	0.033	1.04 (0.64–1.67)	0.883
Previous stroke/TIA/TE	2.01 (1.54–2.62)	<0.001	1.33 (1.00–1.76)	0.046
Abnormal liver function‡	3.47 (2.33–5.17)	<0.001	2.59 (1.68–3.98)	<0.001
Egfr <60 mL·min^{-1}·1.73 m^{-2}§	3.65 (2.62–5.08)	<0.001	2.07 (1.47–2.91)	<0.001
Persistent AF	1.26 (0.97–1.63)	0.080	1.18 (0.89–1.56)	0.250
Diagnosis of AF ≥12 months	1.24 (0.96–1.61)	0.100	1.13 (0.85–1.49)	0.405
Tertiary hospital	0.28 (0.21–0.36)	<0.001	0.56 (0.42–0.75)	<0.001
OAC at penultimate follow-up	0.34 (0.24–0.49)	<0.001	0.49 (0.33–0.72)	<0.001
Inpatients at penultimate follow-up	6.40 (4.92–8.32)	<0.001	4.30 (3.26–5.67)	<0.001
Amiodarone	0.70 (0.38–1.28)	0.247	0.79 (0.42–1.49)	0.473

*Multivariable models were adjusted for age, sex, education status (high school completion), insurance coverage (partial or complete health insurance coverage), body mass index, current smoking and current drinking, history of established CAD, DM, hypertension, hyperlipidemia, CHF, previous bleeding, stroke/transient ischemic attack/thromboembolism, abnormal liver function, estimated glomerular filtration rate of <60 mL/min/1.73 m^2, AF type (persistent AF), time since AF was diagnosed (≥12 months), hospital level (tertiary hospital), oral anticoagulant use, and treatment site (in patients) at the penultimate follow-up. †Established CAD includes myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting. ‡Liver function was obtained in 4955 patients (537 in the amiodarone group and 4418 in the non-AAD group). Abnormal liver function was defined as a serum aspartate aminotransferase or alanine aminotransferase concentration of >120 U/L and total bilirubin concentration of >34.2 μmol/L. §eGFR was obtained in 4918 patients (529 in the amiodarone group and 4389 in the non-AAD group). eGFR (mL·min^{-1}·1.73 m^{-2}) = 186 × (SCr [μmol/L] × 0.0113)$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female), where SCr is the serum creatinine concentration. AAD: Antiarrhythmic drug; AF: Atrial fibrillation; BMI: Body mass index; CAD: Coronary artery disease; CHF: Chronic heart failure; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; OAC: Oral anticoagulants; SD: Standard deviation; TE: Thromboembolism; TIA: Transient ischemic attack.

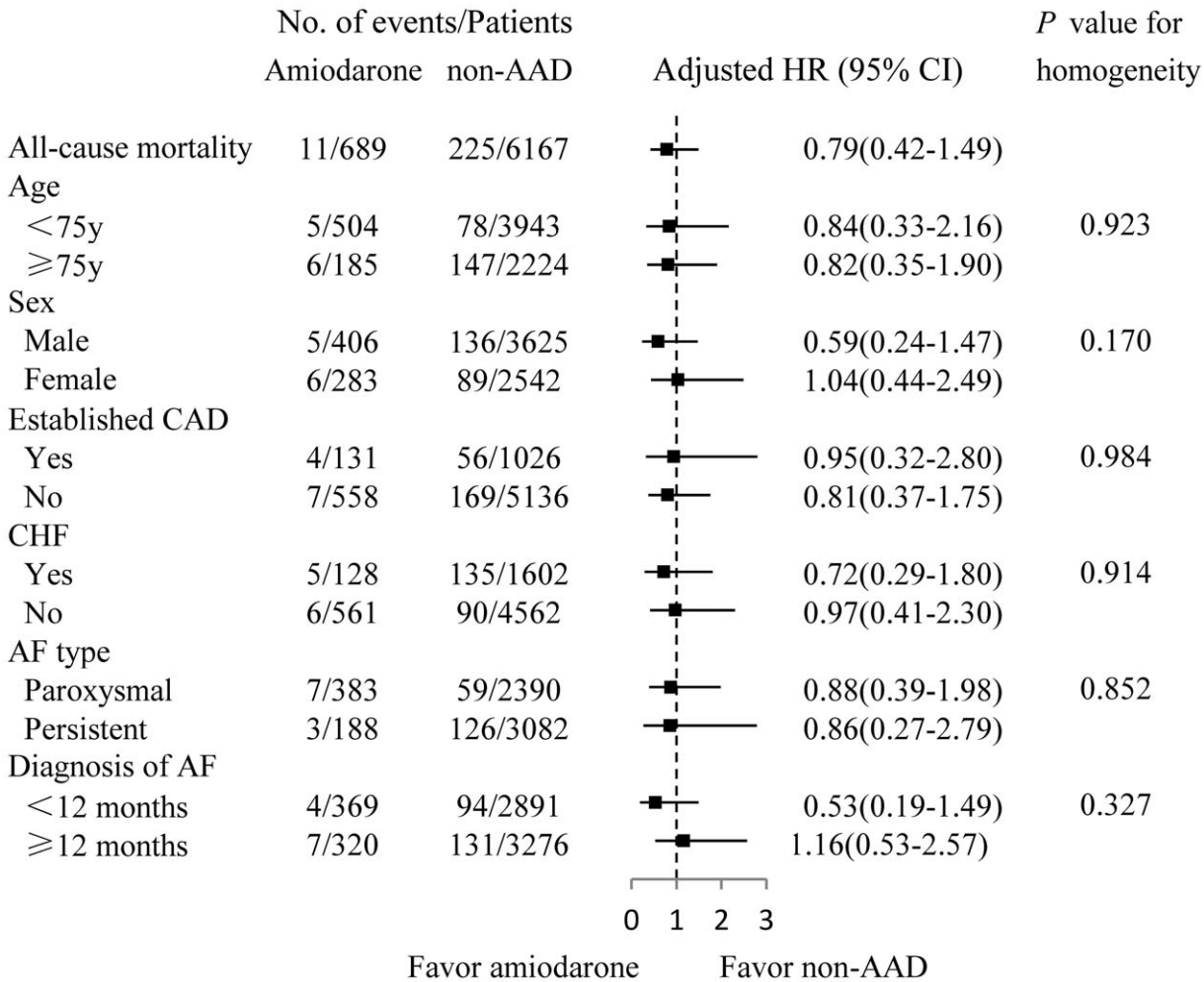

Figure 3: Sub-group analysis for all-cause mortality. Forest plots for all-cause mortality within sub-groups defined by age, sex, prior CAD and CHF, AF type, and time since AF diagnosis among patients with non-valvular AF enrolled in the China-AF registry from 2008 to 2017 by amiodarone use. Models were adjusted for age, sex, education status (high school completion), insurance coverage (partial or complete health insurance coverage), body mass index, smoking and drinking status (current smoking and current drinking), history of established CAD, diabetes mellitus, hypertension, hyperlipidemia, CHF, previous bleeding, stroke/transient ischemic attack/thromboembolism, abnormal liver function, estimated glomerular filtration rate of <60 mL·min^{-1}·1.73 m^{-2}, AF type (persistent AF), time since AF was diagnosed (≥12 months), hospital level (tertiary hospital), oral anticoagulant use, and treatment site (inpatients) at the penultimate follow-up. AAD: Antiarrhythmic drug; AF: Atrial fibrillation; CAD: Coronary artery disease; CHF: Chronic heart failure; CI: Confidence interval; HR: Hazard ratio.

Table 3: Sinus rhythm profile at penultimate follow-up.

Characteristics	Overall ($N=6856$)	Amiodarone group ($n=689$)	Non-AAD group ($n=6167$)	χ^2	P
Sinus rhythm	2859/6856 (41.7)	384/689 (55.7)	2475/6167 (40.1)	62.04	<0.001
Age					
<65 years	1097/2350 (46.7)	181/304 (59.5)	916/2046 (44.8)	23.20	<0.001
≥65 years	1762/4506 (39.1)	203/385 (52.7)	1559/4121 (37.8)	32.81	<0.001
Sex					
Male	1692/4031 (42.0)	234/406 (57.6)	1458/3625 (40.2)	45.46	<0.001
Female	1167/2825 (41.3)	150/283 (53.0)	1017/2542 (40.0)	17.74	<0.001
Established CAD					
Yes	462/1157 (39.9)	70/131 (53.4)	392/1026 (38.2)	11.23	<0.001
No	2394/5694 (42.0)	314/558 (56.3)	2080/5136 (40.5)	51.39	<0.001
CHF					
Yes	631/1730 (36.5)	62/128 (48.4)	569/1602 (35.5)	8.54	0.004
No	2226/5123 (43.5)	322/561 (57.4)	1904/4562 (41.7)	49.87	<0.001
First diagnosis of AF					
<12 months	1534/3260 (47.1)	215/369 (58.3)	1319/2891 (45.6)	20.99	<0.001
≥12 months	1325/3596 (36.8)	169/320 (52.8)	1156/3276 (35.3)	38.48	<0.001

Values are presented as n/N (%). AAD: Antiarrhythmic drug; AF: Atrial fibrillation; CAD: Coronary artery disease; CHF: Chronic heart failure.

AADs and rate-control drugs

In clinical trials, patients who took AADs in combination with rate-control agents were usually classified into the AAD group or rhythm-control group. In the AFFIRM trial,[8] 594 patients assigned to the rhythm-control group crossed over to the rate-control group (actual rate of crossover, 16.7%, 27.3%, and 37.5% after 1, 3, and 5 years, respectively). Sixty-one of these patients had crossed back to the rhythm-control group by the end of the study. An inability to maintain sinus rhythm and drug intolerance were the chief reasons for abandonment of a rhythm-control strategy.

In the present study, rate-control drugs were less commonly used in the amiodarone group than in the non-AAD group. According to the "as treated" definition of exposure, patients in amiodarone group would be censored upon discontinuation of amiodarone. The patients in the non-AAD group were AAD-naive before enrollment and remained off AADs throughout the follow-up period. Thus, crossover between study groups was completely avoided. A combination of both types of pharmacologic agents may often be required in clinical practice, and the choice is not a matter of rate or rhythm control but which agent to try initially.[6]

All-cause mortality

The lack of a significant association between amiodarone use and overall mortality in the present study contrasts with the *post hoc* analysis results of the landmark AFFIRM trial.[19] This difference may be attributed to following important reasons.

First, the patients taking amiodarone therapy in the China-AF Registry study were much younger (65.6 *vs.* 69.7 years), and younger patients might generally benefit preferentially from rhythm control.[27,28]

Second, the effectiveness and safety profile of amiodarone vary with the type and extent of concomitant cardiovascular diseases. Healthier patients might have a better prognosis and might also benefit from AADs. However, a recent study[29] revealed that amiodarone for treatment of AF is associated with increased mortality in patients without structural heart disease and should therefore be avoided or only used as a second-line therapy. Compared with the AFFIRM cohort,[8] the amiodarone group in our study contained a lower proportion of patients with established CAD (19.0% *vs.* 27.6%) and CHF (18.6% *vs.* 22.8%), and inappropriate use of amiodarone will complicate the survival effect in younger and healthier patients.

Third, our study also had fewer number of patients with new-onset AF than the AFFIRM trial (17.1% *vs.* 35.3%), and the prognosis of patients with new-onset AF is worse than that of patients with paroxysmal and persistent AF.[30] In a national health care system population of patients with newly diagnosed AF, the overall use of amiodarone as an early treatment strategy was not associated with mortality.[31]

Fourth, there was variation in the medication use between our study and the AFFIRM trial. Digoxin,[32,33] which has an increased risk of mortality, was significantly less often used by patients in the China-AF Registry study than in the AFFIRM trial (8.9% *vs.* 32.9%).

Fifth, further analysis of the AFFIRM trial[34] revealed that currently available AADs are not associated with improved survival, which suggests that any beneficial antiarrhythmic effects of AADs are offset by their adverse effects. If an effective method for maintaining sinus rhythm with fewer adverse effects were available, it might be beneficial. In our analysis, the rate of sinus rhythm at the penultimate follow-up was significantly higher in the amiodarone group than in the non-AAD group, but the effect of amiodarone was far from complete rhythm control.

The ORBIT-AF Registry[2] revealed a negative survival effect for patients with AF with rhythm control (hazard ratio, 0.87; 95% confidence interval, 0.72–1.04) in contrast to a rate-control strategy without investigating the independent survival effect of amiodarone. An up-to-date randomized trial evaluating the disparity of clinical effects between purely pharmacological rhythm-control and rate-control strategies in patients with AF is warranted; however, such a study can hardly be prospectively conducted with the current rapid development of ablation therapy for patients with AF.[35]

Strengths and limitations

We restricted our sample to patients with AF without reversible causes, including patients who were AAD-naive before registry enrollment; eliminated underlying immortal time bias; adjusted for potential baseline confounders and time-dependent covariates such as OAC use and patient treatment site at the penultimate follow-up. However, residual confounding may have still been present in this study.

Additionally, because our study was observational in nature and all treatment strategies were performed at the local physicians' discretion, we could not infer a definite relationship between amiodarone use and the risk of overall mortality. Effects of other individual AADs on clinical outcomes such as cardiovascular death, stroke, and hospitalization of patients with NVAF were not evaluated because of the small sample size. The cumulative dosage of amiodarone might be associated with its clinical effects and patients' prognosis; however, the exact dose of amiodarone was unavailable in our analysis.

Compared with Western populations, the rates of OAC use for stroke prevention have been lower among Chinese patients with NVAF.[36-38] Fortunately, an improvement was observed in recent years in the China-AF Registry study.[38] Because cardioversion was rarely used, we did not adjust for its effect when we evaluated the association between amiodarone use and the outcome of patients with NVAF.[24] Moreover, we did not account for the severity of AF symptoms in our analyses, which might have also affected patient outcomes.

AF can be regarded as a continuous quantitative entity by considering the AF burden[39,40] rather than considering AF as a binary condition (ie, presence or absence of AF); a higher AF burden is associated with higher risks of stroke and mortality. However, this was not investigated in the current study. Finally, our study primarily involved Chinese patients who resided in Beijing; therefore, the results may not be generalizable to other populations.

Conclusions

Our study indicated that amiodarone use was not significantly associated with a lower risk of 1-year all-cause mortality compared with a non-AAD strategy in "real-world" patients with NVAF.

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Conflicts of interest

None.

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