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 trials⁶⁻¹⁰ and observational studies¹¹⁻¹⁴ 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 management⁵⁻¹⁶ 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
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]

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
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 to 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

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**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.
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 |
|-------------------------|--------------------|----------------------------|--------------------------|--------------------|
| 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 | 6307 (92.1)        | 622 (90.4)                 | 5685 (92.2)              | 2.86† 0.091        |
| 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·min⁻¹·1.73·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)        | 23 (3.3)                   | 341 (5.5)                | 5.94† 0.015        |
| Non-dihydropyridine     | 456 (6.7)          | 42 (6.1)                   | 414 (6.7)                | 0.38† 0.537        |
| 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              | 2718 (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 (%). †P values, ‡x² values. ¹Liver 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 (557 in the amiodarone group and 4361 in the non-AAD group). eGFR (mL·min⁻¹·1.73·m⁻²) = 186 × (SCr [μmol/L] / 0.0113)¹/². Sex and age were adjusted with the Cox proportional hazards model. 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.

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.

follow-up revealed that age, CHF, stroke/TIA/TE, abnormal liver function, eGFR of <60 mL·min⁻¹·1.73·m⁻², and hospitalization at the penultimate follow-up were independent risk factors for all-cause mortality. Body mass index, hyperlipidemia, transient ischaemic attack, 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].
**Profile of AAD use**

With the update of AF management guidelines, 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.

In the AFFIRM trial and a retrospective study of AAD use in England, 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.

![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.](image)

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

| Characteristics                              | Unadjusted HR (95% CI) | P value | Adjusted 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/m²)                                  | 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 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 m², 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]¹·²⁰³ × age³·⁰⁰⁵ × 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.*
Table 3: Sinus rhythm profile at penultimate follow-up.

| Characteristics       | Overall (N = 6856) | Amiodarone group (n = 689) | Non-AAD group (n = 6167) | $\chi^2$ | P     |
|-----------------------|--------------------|----------------------------|--------------------------|---------|-------|
| Sinus rhythm          |                    | 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 abandoning 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.\[8\]

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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