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Use and Outcomes of Antiarrhythmic Therapy in Patients with Atrial Fibrillation Receiving Oral Anticoagulation: Results from the ROCKET AF Trial

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Abstract

Background—Antiarrhythmic drugs (AAD) and anticoagulation are mainstays of atrial fibrillation (AF) treatment.

Objective—We aimed to study the use and outcomes of AAD therapy in anticoagulated AF patients.

Methods—Patients in the ROCKET AF trial (n=14,264) were grouped by AAD use at baseline: amiodarone, other AAD, or no AAD. Multivariable adjustment was performed to compare stroke, bleeding, and death across groups, as well as across treatment assignment (rivaroxaban or warfarin).

Results—Of 14,264 patients randomized, 1681 (11.8%) were treated with an AAD (1144 [8%] with amiodarone, 537 [3.8%] with other AADs). Amiodarone-treated patients were less-often female (38% vs. 48%), had more persistent AF (64% vs. 40%), and more concomitant heart failure (71% vs. 41%) than patients receiving other AADs. Patients receiving no AAD more closely-resembled amiodarone-treated patients. Time in therapeutic range was significantly lower in warfarin-treated patients receiving amiodarone versus no AAD (50% vs. 58%, p<0.0001). Compared with no AAD, neither amiodarone (adjusted HR 0.98, 95% CI 0.74–1.31, p=0.9) nor other AADs (adjusted HR 0.66, 95% CI 0.37–1.17, p=0.15) were associated with increased mortality. Similar results were observed for embolic and bleeding outcomes. Rivaroxaban treatment effects in patients not on an AAD were consistent with the overall trial (primary endpoint adjusted HR 0.82, 95% CI 0.68–0.98, $p_{interaction}$=0.06; safety endpoint adjusted HR 1.12, 95% CI 0.90–1.24, $p_{interaction}$=0.33).

Conclusion—Treatment with AADs was not associated with increased morbidity or mortality in anticoagulated patients with AF. The influence of amiodarone on outcomes in patients receiving rivaroxaban requires further study.

Keywords

atrial fibrillation; antiarrhythmic drugs; rivaroxaban; warfarin; outcomes

INTRODUCTION

The treatment of patients with atrial fibrillation (AF) focuses on 3 primary objectives: (1) prevention of stroke and systemic embolism, (2) control of ventricular rate, and (3)

treatment of symptoms. Medical therapy remains a mainstay for each of these goals, and frequently requires antiarrhythmic drug (AAD) therapy and oral anticoagulation. However, these drug groups present specific management challenges, as well as interactions that may mitigate effectiveness and/or increase the risk of adverse events. This is of particular interest for recently approved novel oral anticoagulants, which may lack many of the interactions that limit vitamin K antagonist (VKA) therapy.

Rivaroxaban is a novel, oral factor Xa inhibitor that is approved for the prevention of stroke or non-central nervous system (CNS) embolism in patients with nonvalvular AF. Its safety and efficacy were demonstrated in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial [1]. However, few data exist regarding the use of rivaroxaban in patients also receiving AAD therapy. The objectives of the current analysis were to: (1) assess clinical outcomes in patients treated with AAD therapy and concomitant anticoagulation, and (2) determine whether the treatment effect of rivaroxaban compared with warfarin varies with AAD therapy.

METHODS

The design of the ROCKET AF study has been described in detail previously (NCT00403767) [2]. Briefly, the ROCKET AF trial was a prospective, randomized, double-blind, placebo-controlled trial of fixed-dose rivaroxaban versus adjusted-dose warfarin for the prevention of stroke or non-CNS systemic embolism in patients with nonvalvular AF at high risk of stroke. Patients underwent clinical assessment at a minimum of every 4 weeks throughout the trial, and this included medication reconciliation and ascertainment of interval events. The use of AAD therapy was at the discretion of the treating physician, and not blinded or randomized.

The present study is a post-hoc analysis including all patients randomized in the trial (intention-to-treat [ITT]), and subsequently grouped according to baseline use of a membrane-active AAD that is used clinically in the treatment of AF. These AADs included amiodarone, dronedarone, sotalol, dofetilide, propafenone, flecainide, quinidine, and disopyramide. After preliminary analyses revealed the majority of AAD use to be amiodarone, the population was stratified by amiodarone use, all other AAD use, and no AAD at baseline. Baseline characteristics and outcomes were compared among these groups. For patients on amiodarone, dosing distribution is presented using most recent reported dose.

Patients were included in the analysis as long as they remained in their baseline group. Patients who either discontinued AAD therapy or changed groups (from amiodarone to other AAD, from other AAD to amiodarone, or from no AAD to any AAD) were censored at the time of therapy change. For patients not on AAD at baseline, exposures of <7 days were ignored. For patients on any AAD at baseline, temporary interruptions of <30 days were ignored. For patients assigned to warfarin, time in therapeutic range (TTR) was calculated for the period of follow-up, during which the patient remained in the same group as baseline (amiodarone, other AAD, no AAD).

OUTCOMES

Clinical endpoints in the ROCKET AF trial have been described previously [2]. The primary endpoint was the occurrence of stroke (ischemic or hemorrhagic) or non-CNS embolism and the primary safety endpoint was the composite of non-major clinically relevant (NMCR) and major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). The present analysis compared outcomes among AAD groups and according to treatment assignment (rivaroxaban or warfarin). Specifically, secondary outcomes of efficacy included composite and individual endpoints of stroke, non-CNS embolism, myocardial infarction (MI), or vascular death, as well as the individual endpoints of all-cause death, non-vascular death, cardiac failure, hospitalization, and emergency department (ED) visits. As in prior analyses, 93 patients were excluded from the efficacy analysis due to violations of Good Clinical Practice at the enrolling center. Safety outcomes were also assessed, and limited to the on-treatment population (patients in the ITT population who received at least 1 study medication dose). These included major bleeding and/or NMCR bleeding.

Statistical Methods

Summary statistics are presented for patterns of AAD use, including proportions of patients, specific drug types, and exposure times. For patients on non-amiodarone AADs, patients who took more than 1 drug were counted for the type taken for the largest proportion of time.

Baseline characteristics are presented as percent (count) for categorical variables and as medians (25th, 75th percentiles) for continuous variables. Because these statistics are intended to describe the analysis population rather than to test any formal hypotheses, no p-values are presented.

For amiodarone dosing, if more than 1 dose was indicated, the last dose was used. Amiodarone dose is reported in categories, but was tested as a continuous variable using Wilcoxon rank sum.

Median (25th, 75th percentile) TTR for each AAD group was calculated, and pairwise comparisons made using Wilcoxon rank sum tests. Only international normalized ratio (INR) values from the time period during which the patient was in the AAD group were used.

For all of the endpoints, event rates (events per 100 patient-years and total events) were generated. Groups were compared using Cox proportional hazards models. Efficacy endpoint models contained the following covariates: age, sex, body mass index, region, diabetes, prior stroke/transient ischemic attack (TIA), vascular disease (MI, peripheral arterial disease, carotid occlusive disease), congestive heart failure, hypertension, chronic obstructive pulmonary disease (COPD), paroxysmal AF, diastolic blood pressure (BP), creatinine clearance (Cockroft-Gault),[3] heart rate, and abstinence from alcohol use. Safety endpoint models contained the following covariates: age; sex; region; prior stroke/TIA; anemia; prior gastrointestinal (GI) bleed; COPD; diastolic BP; creatinine clearance

(Cockroft-Gault) [3]; platelets; albumin; and prior aspirin, VKA, or thienopyridine use. Covariates were imputed where missing using the median for continuous variables and the mode for categorical variables, within groups of patients on or not on an AAD at baseline. Models also contained randomized treatment. Hazard ratios (with 95% confidence interval [CI]) and p-values are presented.

Because either new start or cessation of AAD therapy can be influenced by patient characteristics or intervening events that can also be related to the outcomes, patients were weighted by the inverse probability of continuing in their therapy group (see Supplemental Material).

For the recurrent events of hospitalizations and ED visits, we used the method of Wei, Lin, and Weissfeld for multiple failure times, with a robust sandwich variance estimator [4]. These models incorporated the weighting described above. Due to the small number of patients with repeated events, these models included first and second hospitalizations and first and second ED visits only. A single weighted parameter estimate was used to generate a significance test (Z-score) as well as hazard ratio estimate and CI.

For the primary efficacy and safety endpoints, as well as the specific bleeding endpoints (major, intracranial, GI, fatal, and NMCR), event rates (events per 100 patient-years and total events) were also generated by treatment arm and amiodarone use (vs. no AAD). Patients in the other AAD group were not used in these calculations. Cox models were constructed as above, with the addition of an amiodarone-by-treatment interaction term. Rivaroxaban versus warfarin hazard ratios (95% CIs) were generated for the AAD groups, and the interaction p-value is reported.

All statistical analyses were performed by the Duke Clinical Research Institute (DCRI) using SAS software (version 9.2, SAS Institute, Cary, NC).

RESULTS

Antiarrhythmic Use

Of 14,264 patients randomized in ROCKET AF, 1681 (11.8%) were on an AAD at baseline: 1144 (8.0%) on amiodarone and 537 (3.8%) on other AADs. Among patients on other AADs, 278 (52%) received sotalol, 186 (35%) propafenone, 58 (11%) flecainide, 7 (1.3%) quinidine, and 4 (0.7%) each received disopyramide or dofetilide. No patient was on dronedarone. Derivation of the study population and persistence of therapies are shown in Figure 1. Similar treatment duration and AAD discontinuation rates were observed between patients on amiodarone (median 20 months, 21% discontinuation) and other AADs (median 21 months, 22% discontinuation). Study drug discontinuation (rivaroxaban or warfarin) was similar in those treated with amiodarone versus no AAD (32% for amiodarone, 34% for patients on no AAD, 26% for other AADs).

Patient Characteristics

Characteristics of the patients, stratified by AAD group at baseline (amiodarone, other AAD, or no AAD), are shown in Table 1. Treatment assignment was balanced across AAD groups.

Compared with patients not on AAD at baseline, those on other AADs were more often female (48% vs. 40%), with higher rates of paroxysmal AF (59% vs. 14%), and lower rates of heart failure (41% vs. 63%). Patients on amiodarone more closely resembled those not treated with an AAD, however, they had higher rates of heart failure (71% vs. 63%), less prior VKA use (53% vs. 63%), and less digitalis use (24% vs. 41%) compared with patients not on an AAD.

Among amiodarone-treated patients, over 70% in each group were treated with 200–300 mg daily, followed by 100–150 mg (14% on rivaroxaban, 12% on warfarin), 400–500 mg (9.1% rivaroxaban, 7.9% warfarin), and 600 mg (2.3% rivaroxaban, 3.3% warfarin); doses of <100 mg or >800 mg were used in 1% or less, and there were no differences in dose between the rivaroxaban and warfarin groups (p=0.6). Complete TTR data are shown in Table 2. Among patients assigned to warfarin, the median TTR for patients receiving amiodarone (50% [25th, 75th percentiles: 33, 64%]) was significantly lower when compared with other AADs (61% [45, 74%], p<0.0001) and compared with patients on no AAD (58% [43, 71%], p<0.0001; p=0.16 for other AAD vs. no AAD). Extreme deviations in INR (<1.5 or >4) were uncommon across all 3 groups (<5% of the time).

Outcomes by Antiarrhythmic Group

Adjusted efficacy and safety outcomes are shown in Table 3. Compared with patients on no AAD at baseline, those treated with amiodarone had an increased risk of incident MI (adjusted hazard ratio [HR] 1.76, 95% CI 1.11–2.77, p=0.02), however, they did not have a significantly different risk of any other efficacy or safety outcome. There was no evidence of increased mortality in those treated with amiodarone (HR 0.98, 95% CI 0.74–1.31, p=0.90) (Figure 2). Similarly, patients treated with other AAD agents had a similar risk of major adverse events when compared with patients not on an AAD at baseline. Raw, unadjusted event rates are available in the Supplemental Material (Table S1).

Outcomes by Treatment Assignment

Kaplan-Meier curves for the primary endpoint in each of the 4 groups are shown in Figure 3. Adjusted outcomes comparing rivaroxaban- versus warfarin-assigned patients among patients on amiodarone and not on any AAD at baseline are shown in Table 4. Treatment effects of rivaroxaban versus warfarin in patients not on AAD therapy are consistent with results from the overall trial (stroke or non-CNS embolism adjusted HR 0.82, 95% CI 0.68–0.98, major bleeding adjusted HR 1.05, 95% CI 0.90–1.24). Among patients treated with amiodarone, there were low numbers of stroke or systemic embolic events (34 overall), and low numbers of major bleeding events (43 overall). This yielded wide confidence intervals around hazard estimates (adjusted HR for major bleeding 2.20, 95% CI 0.98–4.91; adjusted HR for stroke or systemic embolism 1.71, 95% CI 0.8–3.65). All tests of interaction between treatment assignment and AAD use were non-significant. In patients receiving amiodarone, there was no significant interaction between treatment assignment (rivaroxaban vs. warfarin) and renal dysfunction, for the primary endpoint (p=0.40).

DISCUSSION

Of the 14,264 patients randomized in the ROCKET AF trial, a minority were treated with an AAD at baseline. However, amiodarone was the most common AAD used and patients treated with amiodarone were among the highest risk. These patterns are consistent with the indications and contraindications for AAD agents. Several of the non-amiodarone AADs require preserved renal function and are contraindicated in structural or ischemic cardiovascular disease. By comparison, amiodarone is often the only agent appropriate for medically-complex patients, or is reserved as the last option in patients with refractory AF due to toxicity profile. This is represented in our data, as the amiodarone group closely resembles those patients not on any AAD rather than those patients on an alternative AAD. Furthermore, the amiodarone group carried a striking proportion of heart failure patients—over 70% had heart failure versus 63% for no AAD and 41% for other AADs. The majority of amiodarone patients were on a dose consistent with clinical treatment of AF (100–300 mg daily), yet we cannot confirm the indication was not ventricular tachycardia. Despite its shortcomings, amiodarone remains the primary AAD for patients with heart failure and AF.

The present analysis represents the largest patient-level study of TTR in those receiving concomitant warfarin and amiodarone, and provides additional insight into the adverse effect of amiodarone on clinical outcomes [5, 6]. These patients had higher rates of both sub- and supra-therapeutic INRs, and TTR is well-known to correlate closely with both bleeding and ischemic outcomes [7]. However, despite the increased overall risk of patients on amiodarone and the lower TTR in these patients, our data did not show increased risk of morbidity or mortality associated with either of the AAD groups (compared with no AAD).

These data may seem counter to results from the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and others, which suggest AADs (amiodarone in particular) increase the risk of morbidity and mortality, specifically non-cardiovascular mortality [8, 9]. Yet, the AFFIRM investigators partially attributed the lower survival to the lower rates of anticoagulation therapy in AAD-treated patients in their cohort. This was not the case in ROCKET AF. All patients received stroke prevention therapy (e.g., anticoagulation), and this suggests that perhaps an element of risk associated with AAD therapy could be reduced by using anticoagulation. This is an important message for clinicians managing patients with AF on AAD therapy as these patients frequently exhibit paroxysmal arrhythmia and may not manifest clinical AF during a visit. There is little evidence for withholding anticoagulation in such patients [10].

In patients receiving no AAD at baseline, hazard ratios of treatment with rivaroxaban versus warfarin were consistent with results from the overall trial. Rivaroxaban was noninferior for the prevention of stroke and demonstrated a significant reduction in fatal and/or intracranial bleeding, at the expense of increased risk of GI bleeding. However, in patients receiving amiodarone, the hazard ratios trend the other way, suggesting increased risk of ischemic and bleeding outcomes in patients assigned to rivaroxaban versus warfarin, and a borderline p-value for the interaction term (0.06). Importantly, interpretation of these results is limited primarily by power. Event rates in these groups are relatively low and yield wide confidence intervals; definitive conclusions about the treatment effects cannot be made. This is

particularly evident in the fact that risk of fatal bleeding and risk of intracranial hemorrhage —events frequently linked—trend in opposite directions.

Additionally, absolute rates of events in patients receiving rivaroxaban are similar irrespective of amiodarone treatment; in contrast, rates of events in patients receiving concomitant warfarin and amiodarone are lower (particularly ischemic events) than in patients receiving warfarin and no AAD. This discrepancy accounts for the difference in hazard ratios between patients treated and not treated with amiodarone. However, in a detailed analysis of TTR in patients receiving warfarin, volatility of INRs in the amiodarone group did not appear to account for this effect.

There is a pharmacokinetic interaction between these drugs: amiodarone is well-known to inhibit both P-glycoprotein and cytochrome P450 3A4 (CYP3A4). The current U.S. Food and Drug Administration label for rivaroxaban states that patients with renal impairment taking P-glycoprotein and weak-to-moderate CYP3A4 inhibitors (like amiodarone) may have increases in exposure, which may increase bleeding risk. The ROCKET AF trial protocol did not specifically dose adjust for such interactions [11]. Cardiovascular drugs affected by the P-glycoprotein system are well described and can alter clinical outcomes. Furthermore, such an effect is not limited to rivaroxaban—all oral anticoagulants, including warfarin, exhibit such interactions to varying degrees [12]. Therefore, while there remains the potential for clinically significant interactions between amiodarone and rivaroxaban, further studies are necessary to precisely define such an effect.

Lastly, our data highlight the limited use of rhythm control therapies in patients with AF, who are at high risk of stroke. A minority of patients in the ROCKET AF trial had a prior catheter ablation for AF, and only 79 underwent such a procedure during the trial.[13] Our analysis shows that only a minority received AAD therapy; and while amiodarone can be highly effective, it is also the most toxic AAD. Similar rates were observed in the ARISTOTLE trial – approximately 1 in 10 patients was treated with amiodarone.[14] While these data may not reflect trends in the broader, general AF population, rhythm control strategies in such high-risk patients warrant further investigation.[15]

LIMITATIONS

The current study represents a post-hoc, subgroup analysis of the ROCKET AF trial. As such, it should be interpreted as hypothesis-generating. Treatment with AAD was not randomized and thus there may exist residual and/or unmeasured confounding in comparisons among AAD groups. Furthermore, the number of patients receiving amiodarone, although substantial (>1100), was a fraction of the overall trial, and thus may lack the power to precisely measure the treatment effect, if any, of rivaroxaban compared with warfarin. Lastly, we cannot exclude the use of amiodarone for ventricular arrhythmias.

CONCLUSIONS

A minority of patients in ROCKET AF were treated with an AAD. However, AAD therapy was not associated with worse clinical outcomes in anticoagulated patients with AF.

Addition of amiodarone to warfarin significantly reduces TTR, and the effect of amiodarone on rivaroxaban effectiveness requires additional investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AAD	antiarrhythmic drug
AF	atrial fibrillation
BP	blood pressure
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
ED	emergency department
GI	gastrointestinal
HR	hazard ratio
INR	international normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention to treat
MI	myocardial infarction
NMCR	non-major clinically relevant
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
TIA	transient ischemic attack
TTR	time in therapeutic range
VKA	vitamin K antagonist

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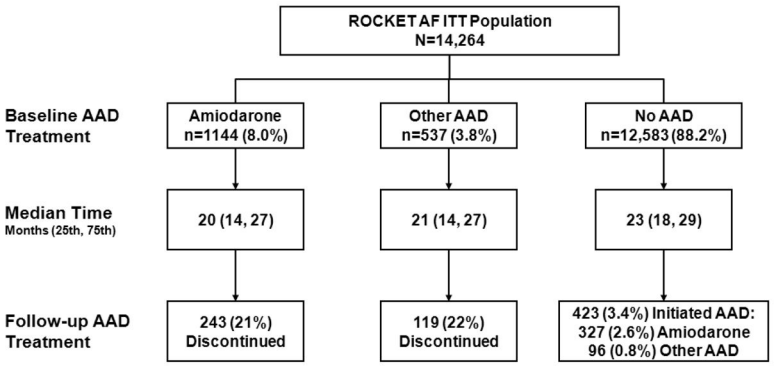
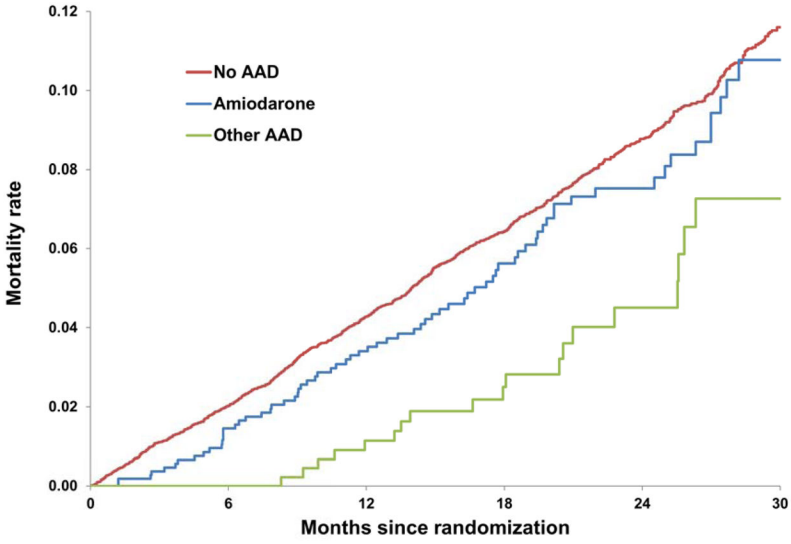


Figure 1.

Derivation of study population and persistence of AAD therapy. Patients were stratified by baseline AAD use: amiodarone, other AAD, or no AAD. AAD=antiarrhythmic drug; ITT=intention-to-treat; ROCKET AF= Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

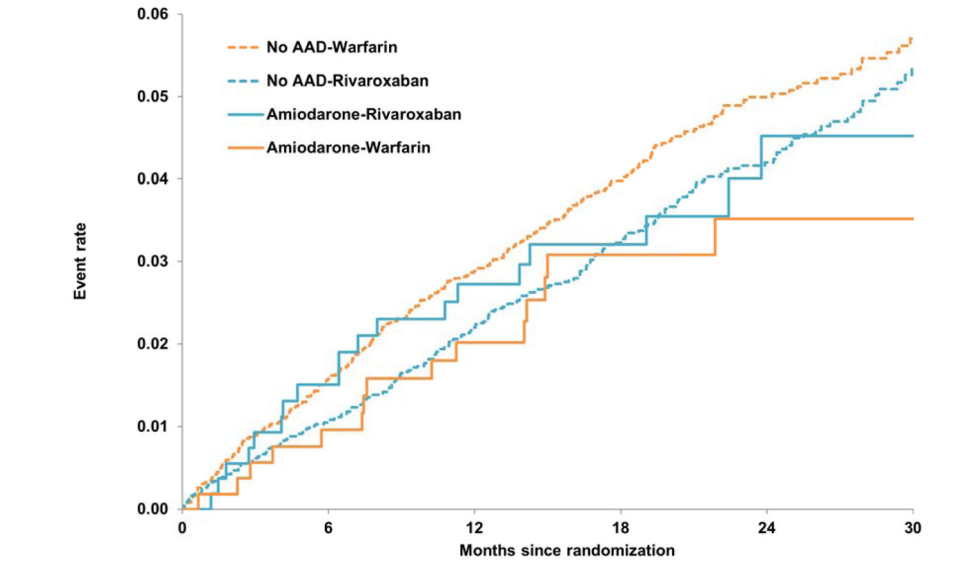


No AAD	12503	11865	11247	8201	4974	2132
Amiodarone	1132	991	904	624	359	118
Other AAD	536	464	422	305	169	69

Figure 2.

Kaplan-Meier curves for all-cause mortality, by AAD use at baseline. P=NS for all 3 pair-wise comparisons, by multivariable Cox models.

AAD=antiarrhythmic drug.



No AAD-Warfarin	6273	5886	5531	4022	2432	1041
No AAD-Rivaroxaban	6230	5879	5546	4009	2412	1024
Amiodarone-Rivaroxaban	567	499	456	308	178	56
Amiodarone-Warfarin	565	485	437	305	171	57

Figure 3.

Kaplan-Meier curves for stroke or non-CNS embolism in patients randomized to rivaroxaban versus warfarin, grouped by amiodarone use at baseline (vs. no AAD). AAD=antiarrhythmic drug; CNS=central nervous system.

Table 1

Baseline characteristics

	Amiodarone (N=1144)	Other AAD (N=537)	No AAD (N=12,583)
Treatment assignment			
Rivaroxaban	50.0% (572)	53.1% (285)	49.9% (6274)
Warfarin	50.0% (572)	46.9% (252)	50.1% (6309)
Age, yrs	70 (61, 77)	70 (63, 76)	73 (66, 78)
Female	38.4% (439)	47.5% (255)	39.5% (4966)
Atrial fibrillation			
New onset	1.8% (21)	0.2% (1)	1.4% (180)
Paroxysmal	34.4% (393)	59.4% (319)	14.3% (1802)
Persistent	63.8% (730)	40.4% (217)	84.2% (10601)
$CHADS_2$ score, mean (SD)	3.5 (0.9)	3.3 (0.9)	3.5 (0.9)
$CHADS_2$ score			
1	0	0	<0.1% (3)
2	10.5% (120)	16.6% (89)	13.1% (1650)
3	42.7% (488)	47.3% (254)	43.5% (5474)
4	32.3% (370)	25.9% (139)	28.5% (3582)
5	12.9% (148)	8.8% (47)	12.9% (1618)
6	1.6% (18)	1.5% (8)	2.0% (256)
Presenting characteristics			
BMI, kg/m^2	28.9 (25.7, 32.7)	28.1 (25.0, 31.6)	28.1 (25.1, 31.9)
Systolic BP, mm Hg	130 (120, 140)	130 (120, 140)	130 (120, 140)
Diastolic BP, mm Hg	80 (72, 86)	80 (70, 84)	80 (70, 85)
Heart rate, beats/min	75 (65, 86)	70 (62, 80)	76 (68, 86)
Creatinine clearance,* mL/min	67 (52, 87)	74 (57, 98)	67 (52, 86)
Baseline comorbidities			
Prior ablation for AF	2.8% (32)	5.8% (31)	2.1% (258)
Prior stroke, TIA, or non-CNS embolism	56.2% (643)	67.6% (363)	54.1% (6805)
PAD	5.9% (68)	3.4% (18)	6.0% (753)
Hypertension	92.9% (1063)	86.2% (463)	90.5% (11384)
Diabetes	39.9% (457)	33.9% (182)	40.2% (5056)
Prior MI	16.9% (193)	11.0% (59)	17.6% (2216)
CHF	71.1% (813)	41.3% (222)	62.6% (7873)
COPD	10.7% (122)	8.4% (45)	10.6% (1330)
Medications			
Prior VKA use	52.5% (601)	64.4% (346)	63.2% (7957)
Prior chronic ASA use	42.5% (486)	32.8% (176)	36.1% (4543)
ACE-I/ARB at baseline	76.9% (880)	66.3% (356)	74.3% (9347)
Beta blocker at baseline	50.2% (574)	78.6% (422)	65.6% (8254)
Digitalis at baseline	24.0% (274)	15.3% (82)	40.6% (5112)
Diuretic at baseline	60.7% (694)	41.9% (225)	60.2% (7571)

Continuous variables are shown as median (25th, 75th percentiles), unless otherwise noted.

* Creatinine clearance calculated according to the Cockcroft-Gault equation.

AAD=antiarrhythmic drug; ACE-I=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ASA=aspirin; BMI=body mass index; BP=blood pressure; CHF=congestive heart failure; CNS=central nervous system; COPD=chronic obstructive pulmonary disease; MI=myocardial infarction; PAD=peripheral arterial disease; SD=standard deviation; TIA=transient ischemic attack; VKA=vitamin K antagonist.

Table 2

Anticoagulation control by AAD group among warfarin-treated patients

	Amiodarone (n=558)	Other AAD (n=246)	No AAD (n=6221)
TTR, INR 2–3	50 (33, 64)	61 (45, 74)	58 (43, 71)
Time INR<2	27 (16, 45)	21 (11, 37)	24 (13, 39)
Time INR 1.5–<2 (%)	20 (12, 29)	15 (8, 24)	18 (11, 28)
Time INR 1–<1.5 (%)	4 (0, 13)	2 (0, 9)	3 (0, 9)
Time INR <1 (%)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Time INR>3	16 (9, 26)	13 (5, 21)	13 (7, 21)
Time INR >3–4 (%)	12 (6, 19)	11 (5, 17)	11 (5, 17)
Time INR >4–5 (%)	2 (0, 4)	0 (0, 2)	1 (0, 3)
Time INR >5 (%)	0 (0, 1)	0 (0, 0)	0 (0, 0)

Data presented as median percent time (25th, 75th percentiles). P-values for TTR: amiodarone vs. no AAD = <0.0001; other AAD vs. no AAD = 0.16; and amiodarone vs. other AAD <0.0001 (from pairwise Wilcoxon rank sum tests). A total of 5% of patients had at least one INR value <1; among these patients, the median amount of time spent in this range was 1.1%. A total of 29% of patients had at least one INR value >5; among these patients, the median amount of time spent in this range was 1.6%.

AAD=antiarrhythmic drug; INR=international normalized ratio; TTR=time in therapeutic range.

Table 3

Adjusted outcomes by AAD use at baseline

	Amiodarone vs. No AAD		Other AAD vs. No AAD		Amiodarone vs. Other AAD	
	HR (95% CI)	**P-Value**	**HR (95% CI)**	**P-Value**	**HR (95% CI)**	**P-Value**
Efficacy outcomes						
All-cause death	0.98 (0.74, 1.31)	0.90	0.66 (0.37, 1.17)	0.15	1.49 (0.78, 2.84)	0.22
Vascular death	0.89 (0.61, 1.31)	0.56	0.60 (0.27, 1.34)	0.21	1.48 (0.61, 3.61)	0.39
Non-vascular death	1.14 (0.76, 1.71)	0.52	0.74 (0.32, 1.70)	0.48	1.54 (0.62, 3.81)	0.35
Stroke or non-CNS embolism	1.17 (0.76, 1.81)	0.48	0.57 (0.26, 1.22)	0.15	2.06 (0.87, 4.90)	0.10
Stroke, non-CNS embolism, MI, or vascular death	1.06 (0.80, 1.39)	0.69	0.79 (0.49, 1.26)	0.32	1.34 (0.78, 2.32)	0.29
Stroke	1.03 (0.67, 1.57)	0.90	0.59 (0.26, 1.31)	0.20	1.75 (0.73, 4.21)	0.21
Non-CNS embolism	2.34 (0.83, 6.59)	0.11	0.56 (0.08, 3.90)	0.55	4.21 (0.54, 32.5)	0.17
MI	1.76 (1.11, 2.77)	**0.02**	1.35 (0.63, 2.92)	0.44	1.30 (0.53, 3.17)	0.56
Cardiac failure	1.17 (0.95, 1.44)	0.14	0.86 (0.52, 1.43)	0.56	1.36 (0.79, 2.35)	0.27
Hospitalization	1.13 (0.92, 1.39)	0.25	1.06 (0.79, 1.41)	0.70	1.06 (0.75, 1.49)	0.75
ED visit	0.91 (0.78, 1.07)	0.26	1.21 (0.96, 1.51)	0.10	0.76 (0.58, 1.00)	0.99
Safety outcomes						
Major or NMCR bleeding	0.98 (0.81, 1.18)	0.81	0.83 (0.63, 1.09)	0.18	1.18 (0.85, 1.64)	0.32
Major bleeding	0.90 (0.61, 1.31)	0.58	0.77 (0.45, 1.32)	0.34	1.17 (0.61, 2.23)	0.64
NMCR bleeding	0.99 (0.80, 1.21)	0.90	0.80 (0.59, 1.09)	0.16	1.23 (0.86, 1.77)	0.25

AAD=antiarrhythmic drug; CI=confidence interval; CNS=central nervous system; ED=emergency department; HR=hazard ratio; MI=myocardial infarction; NMCR=non-major clinically relevant.

Table 4

Adjusted outcomes of rivaroxaban versus warfarin by amiodarone use

	Amiodarone			No AAD			Interaction P-Value (Amiodarone and Treatment)
	Rivaroxaban Events/100 pt-yrs (Total Events)	Warfarin Events/100 pt-yrs (Total Events)	Rivaroxaban vs. Warfarin HR (95% CI)	Rivaroxaban Events/100 pt-yrs (Total Events)	Warfarin Events/100 pt-yrs (Total Events)	Rivaroxaban vs. Warfarin HR (95% CI)	
Stroke or non-CNS embolism Bleeding	2.14 (19)	1.74 (15)	1.71 (0.80, 3.65)	2.16 (237)	2.54 (279)	**0.82 (0.68, 0.98)**	0.063
Major or NMCR	15.90 (108)	13.82 (92)	1.35 (0.94, 1.92)	15.00 (1284)	14.53 (1261)	**1.12 (1.00, 1.25)**	0.33
Major bleeding	3.84 (29)	1.88 (14)	2.20 (0.98, 4.91)	3.61 (343)	3.58 (347)	1.05 (0.90, 1.24)	0.078
ICH	0.52 (4)	0.27 (2)	2.42 (0.37, 16.0)	0.50 (48)	0.78 (77)	**0.61 (0.42, 0.88)**	0.16
GI	1.70 (13)	0.40 (3)	4.58 (0.92, 22.8)	1.75 (168)	1.14 (112)	**1.68 (1.30, 2.18)**	0.23
Fatal	0.13 (1)	0.40 (3)	0.48 (0.06, 3.83)	0.25 (24)	0.50 (49)	**0.49 (0.30, 0.80)**	0.98
NMCR bleeding	12.28 (85)	12.03 (81)	1.24 (0.84, 1.83)	11.92 (1035)	11.28 (993)	**1.15 (1.01, 1.31)**	0.71

AAD=antiarrhythmic drug; CI=confidence interval; CNS=central nervous system; GI=gastrointestinal; HR=hazard ratio; ICH=intracranial hemorrhage; NMCR=non-major clinically relevant.