Use and outcomes of antiarrhythmic therapy in patients with atrial fibrillation receiving oral anticoagulation: Results from the ROCKET AF trial

Benjamin A. Steinberg, MD,[*] Anne S. Hellkamp, MS,[*] Yuliya Lokhnygina, PhD,[*] Jonathan L. Halperin, MD,[†] Günter Breithardt, MD,[‡] Rod Passman, MD,[§] Graeme J. Hankey, MD,[‖] Manesh R. Patel, MD,[*] Richard C. Becker, MD,[¶] Daniel E. Singer, MD,[#] Werner Hacke, MD, PhD,[**] Scott D. Berkowitz, MD,[††] Christopher C. Nessel, MD,[‡‡] Kenneth W. Mahaffey, MD,[§§] Keith A.A. Fox, MBChB,[‖‖] Robert M. Califf, MD,[¶¶] Jonathan P. Piccini, MD, MHS, FHRS,[*] on behalf of the ROCKET AF Steering Committee and Investigators

From the [*]Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina, [†]Cardiovascular Institute, Mount Sinai Medical Center, New York, New York, [‡]Department of Cardiovascular Medicine, Hospital of the University of Münster, Münster, Germany, [§]Northwestern University Feinberg School of Medicine, Chicago, Illinois, [‖]School of Medicine and Pharmacology, The University of Western Australia, Crawley, Australia, [¶]University of Cincinnati College of Medicine, Cincinnati, Ohio, [#]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, [**]Ruprecht-Karls-University, Heidelberg, Germany, [††]Bayer HealthCare Pharmaceuticals, Montville, New Jersey, [‡‡]Janssen Research & Development LLC, Raritan, New Jersey, [§§]Department of Medicine, Stanford University, Stanford, California, [‖‖]University of Edinburgh and Royal Infirmary of Edinburgh, Edinburgh, United Kingdom, and [¶¶]Duke Translational Medicine Institute, Duke University Medical Center, Durham, North Carolina.

BACKGROUND Antiarrhythmic drugs (AADs) and anticoagulation are mainstays of atrial fibrillation (AF) treatment.

OBJECTIVE To study the use and outcomes of AAD therapy in anticoagulated patients with AF.

METHODS Patients in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial (N = 14,264) were stratified by AAD use at baseline: amiodarone, other AAD, or no AAD. Multivariable adjustment was performed to compare stroke, bleeding, and death across AAD 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 and 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 were 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 than in those receiving no AAD (50% vs 58%; $P < .0001$). Compared with no AAD, neither amiodarone (adjusted hazard ratio [HR] 0.98; 95% confidence interval [CI] 0.74–1.31; $P = .9$) nor other AADs (adjusted HR 0.66; 95% CI 0.37–1.17; $P = .15$) were associated with increased mortality. Similar results were observed for embolic and bleeding outcomes. Treatment effects of rivaroxaban vs warfarin in patients receiving no AAD were consistent with results from the overall trial (primary end point: adjusted HR 0.82; 95% CI 0.68–0.98; $P_{interaction} = .06$; safety end point: adjusted HR 1.12; 95% CI 0.90–1.24; $P_{interaction} = .33$).

CONCLUSION Treatment with AADs was not associated with increased morbidity or mortality in anticoagulated patients with AF. The effect of amiodarone on outcomes in patients receiving rivaroxaban requires further investigation.

KEYWORDS Atrial fibrillation; Antiarrhythmic drugs; Rivaroxaban; Warfarin; Outcomes

ABBREVIATIONS **AAD** = antiarrhythmic drug; **AF** = atrial fibrillation; **CI** = confidence interval; **CNS** = central nervous system; **ED** = emergency department; **GI** = gastrointestinal; **HR** = hazard ratio; **INR** = international normalized ratio; **MI** = myocardial infarction; **NMCR** = nonmajor 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; **TTR** = time in therapeutic range; **VKA** = vitamin K antagonist

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Address reprint requests and correspondence: Dr Benjamin A. Steinberg, Duke Clinical Research Institute, Duke University Medical Center, PO Box 17969, Durham, NC 27715. E-mail address: benjamin.steinberg@dm.duke.edu.

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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 Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial.[1] However, few data exist regarding the use of rivaroxaban in patients also receiving AAD therapy. The objectives of the present analysis were (1) to assess clinical outcomes in patients treated with AAD therapy and concomitant anticoagulation and (2) to determine whether the treatment effect of rivaroxaban compared with warfarin varies with AAD therapy.

Methods

The design of the ROCKET AF trial has been described in detail previously (ClinicalTrials.gov: unique identifier NCT00403767).[2] Briefly, the ROCKET AF trial was a prospective, randomized, double-blind, placebo-controlled trial of fixed-dose rivaroxaban vs adjusted-dose warfarin for the prevention of stroke or non-CNS systemic embolism in patients with nonvalvular AF who are 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 stratified 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 that amiodarone was the most common AAD used, 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 receiving amiodarone, dosing distribution is presented using most recently 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 receiving no AAD at baseline, exposures of less than 7 days were ignored. For patients receiving any AAD at baseline, temporary interruptions of less than 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, and no AAD).

Outcomes

Clinical endpoints in the ROCKET AF trial have been described previously.[2] The primary end point was the occurrence of stroke (ischemic or hemorrhagic) or non-CNS embolism, and the primary safety end point was the composite of nonmajor clinically relevant (NMCR) and major bleeding as defined by the International Society on Thrombosis and Haemostasis. 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 end points of stroke, non-CNS embolism, myocardial infarction (MI), or vascular death, as well as the individual end points of all-cause death, non–vascular death, cardiac failure, hospitalization, and emergency department (ED) visits. As in prior analyses, 93 (0.6%) patients were excluded from the efficacy analysis owing 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 intention-to-treat 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. Among patients receiving non-amiodarone AADs, patients who took more than 1 drug were counted for the type taken for the largest amount of time.

Baseline characteristics are presented as count (percentage) for categorical variables and as median (25th, 75th percentile) 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 by using the Wilcoxon rank sum test.

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

For all the end points, event rates (events per 100 patient-years and total events) were generated. Groups were compared by using Cox proportional hazards models. Efficacy end point models consisted of the following covariates: age, sex, body mass index, region, diabetes, prior stroke/transient ischemic attack, vascular disease (MI, peripheral arterial disease, and carotid occlusive disease), congestive heart failure, hypertension, chronic obstructive pulmonary disease, paroxysmal AF, diastolic blood pressure, creatinine clearance (calculated by using the Cockcroft-Gault equation),[3] heart rate, and abstinence from alcohol use. Safety end point models contained the following covariates: age, sex, region, prior stroke/transient ischemic attack, anemia, prior gastrointestinal (GI) bleed, chronic obstructive pulmonary disease, diastolic blood pressure, creatinine clearance (calculated by using the Cockcroft-Gault equation),[3] platelets, albumin, and prior aspirin, VKA, or thienopyridine use. Covariates were imputed, where missing, by using the median for continuous variables and the mode for categorical variables within groups of patients receiving or not receiving an AAD at baseline. Models also contained randomized treatment. Hazard ratios (HRs) with 95% confidence intervals (CIs) and *P* values are presented.

Because either new start or cessation of AAD therapy can be affected 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 the Online Supplemental Material).

For the recurrent events of hospitalizations and ED visits, we used the method of Wie et al[4] for multiple failure times with a robust sandwich variance estimator. These models incorporated the weighting described above. Owing 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 an HR estimate and CI.

For the primary efficacy and safety end points as well as the specific bleeding end points (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 vs warfarin HRs (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 using SAS software (version 9.2, SAS Institute, Cary, NC).

Results

Antiarrhythmic use

Of 14,264 patients randomized in the ROCKET AF, 1681 (11.8%) were treated with an AAD at baseline: 1144 (8.0%) with amiodarone and 537 (3.8%) with other AADs. Of 537 patients treated with 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 received dronedarone. The derivation of the study population and persistence of AAD therapies are shown in Figure 1. Similar treatment duration and AAD discontinuation rates were observed in patients receiving amiodarone (median 20 months; 21% discontinuation) and those receiving other AADs (median 21 months; 22% discontinuation). Study drug discontinuation (rivaroxaban or warfarin) was similar in those receiving amiodarone and those receiving no AAD (32% for patients receiving amiodarone, 34% for patients receiving no AAD, and 26% for patients receiving other AADs).

Patient characteristics

Characteristics of the patients, stratified by AAD use at baseline (amiodarone, other AAD, or no AAD), are summarized in Table 1. Treatment assignment was balanced across AAD groups. Compared with patients receiving no AAD at baseline, those receiving other AADs were more often female (48% vs 40%) and had higher rates of paroxysmal AF (59% vs 14%) and lower rates of heart failure (41% vs 63%). Patients treated with amiodarone more closely resembled those not treated with an AAD; however,

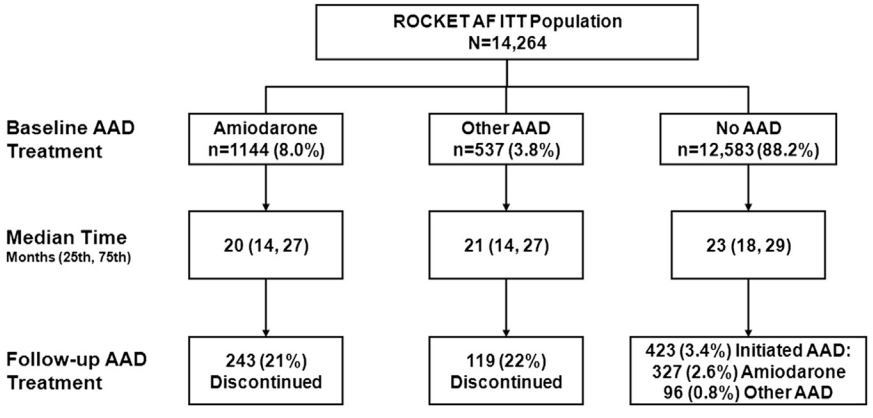


Figure 1 Derivation of study population and persistence of AAD therapies. Patients were stratified by AAD use at baseline: amiodarone, other AAD, or no AAD. AAD = antiarrhythmic drug; ITT = intention to treat; ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

Table 1 Baseline characteristics

Characteristic	Amiodarone (n = 1144)	Other AAD (n = 537)	No AAD (n = 12,583)
Treatment assignment			
Rivaroxaban	572 (50.0)	285 (53.1)	6274 (49.9)
Warfarin	572 (50.0)	252 (46.9)	6309 (50.1)
Age (y)	70 (61, 77)	70 (63, 76)	73 (66, 78)
Sex: female	439 (38.4)	255 (47.5)	4966 (39.5)
Atrial fibrillation			
New onset	21 (1.8)	1 (0.2)	180 (1.4)
Paroxysmal	393 (34.4)	319 (59.4)	1802 (14.3)
Persistent	730 (63.8)	217 (40.4)	10,601 (84.2)
$CHADS_2$ score	3.5 ± 0.9	3.3 ± 0.9	3.5 ± 0.9
$CHADS_2$ score			
1	0	0	3 (<0.1)
2	120 (10.5)	89 (16.6)	1650 (13.1)
3	488 (42.7)	254 (47.3)	5474 (43.5)
4	370 (32.3)	139 (25.9)	3582 (28.5)
5	148 (12.9)	47 (8.8)	1618 (12.9)
6	18 (1.6)	8 (1.5)	256 (2.0)
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	32 (2.8)	31 (5.8)	258 (2.1)
Prior stroke, TIA, or non-CNS embolism	643 (56.2)	363 (67.6)	6805 (54.1)
PAD	68 (5.9)	18 (3.4)	753 (6.0)
Hypertension	1063 (92.9)	463 (86.2)	11,384 (90.5)
Diabetes	457 (39.9)	182 (33.9)	5056 (40.2)
Prior MI	193 (16.9)	59 (11.0)	2216 (17.6)
CHF	813 (71.1)	222 (41.3)	7873 (62.6)
COPD	122 (10.7)	45 (8.4)	1330 (10.6)
Medications			
Prior VKA use	601 (52.5)	346 (64.4)	7957 (63.2)
Prior chronic ASA use	486 (42.5)	176 (32.8)	4543 (36.1)
ACE-I/ARB at baseline	880 (76.9)	356 (66.3)	9347 (74.3)
β-Blocker at baseline	574 (50.2)	422 (78.6)	8254 (65.6)
Digitalis at baseline	274 (24.0)	82 (15.3)	5112 (40.6)
Diuretic at baseline	694 (60.7)	225 (41.9)	7571 (60.2)

Data are presented as median (25th, 75th percentile), mean ± SD, or n (%).

AAD = antiarrhythmic drug; ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; 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; TIA = transient ischemic attack; VKA = vitamin K antagonist.

*Creatinine clearance calculated by using the Cockcroft-Gault equation.

they had higher rates of heart failure (71% vs 63%), less prior VKA use (53% vs 63%), and less digitalis use (24% vs 41%) than did patients not treated with an AAD.

Among amiodarone-treated patients, more than 70% in each group were treated with 200–300 mg daily, followed by 100–150 mg (14% receiving rivaroxaban and 12% receiving warfarin), 400–500 mg (9.1% rivaroxaban and 7.9% warfarin), and 600 mg (2.3% rivaroxaban and 3.3% warfarin); doses of less than 100 or greater than 800 mg were used in 1% or less, and there were no differences in dose between the rivaroxaban and warfarin groups ($P = .6$). Complete TTR data are given in Table 2. Among patients assigned to warfarin, the median TTR for patients receiving amiodarone (50% [25th, 75th percentile 33%, 64%]) was significantly lower than that for those receiving other AADs (61% [45%, 74%]; $P < .0001$) and for patients receiving no AAD (58% [43%, 71%]; $P < .0001$; $P = .16$ 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 stratified by the antiarrhythmic group

Adjusted efficacy and safety outcomes are summarized in Table 3. Compared with patients treated with no AAD at baseline, those treated with amiodarone had an increased risk of incident MI (adjusted HR 1.76; 95% CI 1.11–2.77; $P = .02$); 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; $P = .90$;

Table 2 Anticoagulation control by the 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 are presented as median percent time (25th, 75th percentile). *P* values for TTR: amiodarone vs no AAD, <.0001; other AAD vs no AAD, .16; and amiodarone vs other AAD, <.0001 (calculated by using pairwise Wilcoxon rank sum tests). A total of 5% of the patients had at least 1 INR value <1; among these patients, the median amount of time spent in this range was 1.1%. A total of 29% of the patients had at least 1 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.

(Figure 2). Furthermore, patients treated with other AADs and patients not treated with an AAD at baseline had a similar risk of major adverse events. Raw (unadjusted) event rates are available in the Online Supplemental Material (see Online Supplemental Table 1).

Outcomes stratified by treatment assignment

Kaplan-Meier curves for the primary end point in each of the 4 groups are shown in Figure 3. Adjusted outcomes comparing rivaroxaban- and warfarin-treated patients among patients treated with amiodarone and those not treated with any AAD at baseline are shown in Table 4. Treatment effects of rivaroxaban vs warfarin in patients not receiving 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). In 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 CIs around hazard estimates (major bleeding: adjusted HR 2.20; 95% CI 0.98–4.91; stroke or systemic embolism: adjusted HR 1.71; 95% CI 0.8–3.65). All tests of interaction between treatment assignment and AAD use were nonsignificant. In patients receiving amiodarone, there was no significant interaction between treatment assignment (rivaroxaban vs warfarin) and renal dysfunction for the primary end point ($P = .40$).

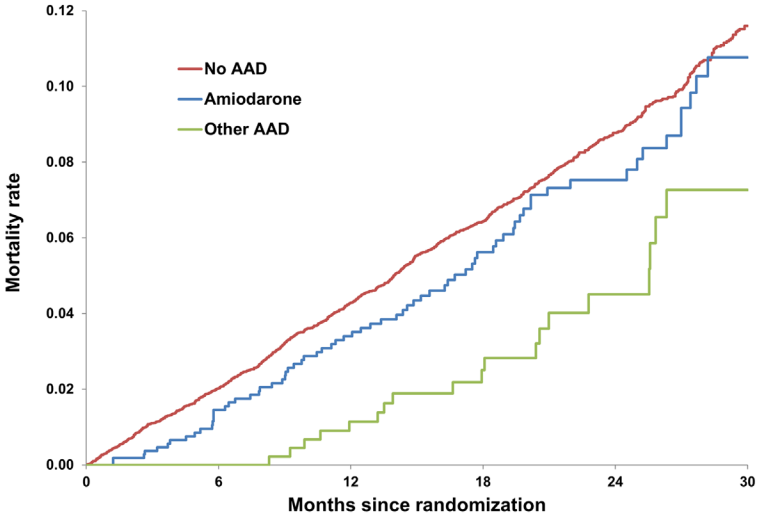
Discussion

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 AADs. 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 drug appropriate for medically complex patients or is reserved as the last option in patients with refractory AF owing to the toxicity profile. This is represented in our data, as the amiodarone group closely resembles those patients not receiving any AAD rather than those patients receiving an alternative AAD. Furthermore, the amiodarone group consisted of a striking proportion of patients with heart failure: more than 70% had heart failure vs 63% for no AAD and 41% for other AADs. The majority of amiodarone-treated patients were receiving a dose consistent with the clinical treatment of AF (100–300 mg daily); however,

Table 3 Adjusted outcomes stratified by AAD use at baseline

	Amiodarone vs no AAD		Other AAD vs no AAD		Amiodarone vs other AAD	
Outcome	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Efficacy outcomes						
All-cause death	0.98 (0.74–1.31)	.90	0.66 (0.37–1.17)	.15	1.49 (0.78–2.84)	.22
Vascular death	0.89 (0.61–1.31)	.56	0.60 (0.27–1.34)	.21	1.48 (0.61–3.61)	.39
Non–vascular death	1.14 (0.76–1.71)	.52	0.74 (0.32–1.70)	.48	1.54 (0.62–3.81)	.35
Stroke or non-CNS embolism	1.17 (0.76–1.81)	.48	0.57 (0.26–1.22)	.15	2.06 (0.87–4.90)	.10
Stroke, non-CNS embolism, MI, or vascular death	1.06 (0.80–1.39)	.69	0.79 (0.49–1.26)	.32	1.34 (0.78–2.32)	.29
Stroke	1.03 (0.67–1.57)	.90	0.59 (0.26–1.31)	.20	1.75 (0.73–4.21)	.21
Non-CNS embolism	2.34 (0.83–6.59)	.11	0.56 (0.08–3.90)	.55	4.21 (0.54–32.5)	.17
MI	1.76 (1.11–2.77)	**.02**	1.35 (0.63–2.92)	.44	1.30 (0.53–3.17)	.56
Cardiac failure	1.17 (0.95–1.44)	.14	0.86 (0.52–1.43)	.56	1.36 (0.79–2.35)	.27
Hospitalization	1.13 (0.92–1.39)	.25	1.06 (0.79–1.41)	.70	1.06 (0.75–1.49)	.75
ED visit	0.91 (0.78–1.07)	.26	1.21 (0.96–1.51)	.10	0.76 (0.58–1.00)	.99
Safety outcomes						
Major or NMCR bleeding	0.98 (0.81–1.18)	.81	0.83 (0.63–1.09)	.18	1.18 (0.85–1.64)	.32
Major bleeding	0.90 (0.61–1.31)	.58	0.77 (0.45–1.32)	.34	1.17 (0.61–2.23)	.64
NMCR bleeding	0.99 (0.80–1.21)	.90	0.80 (0.59–1.09)	.16	1.23 (0.86–1.77)	.25

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



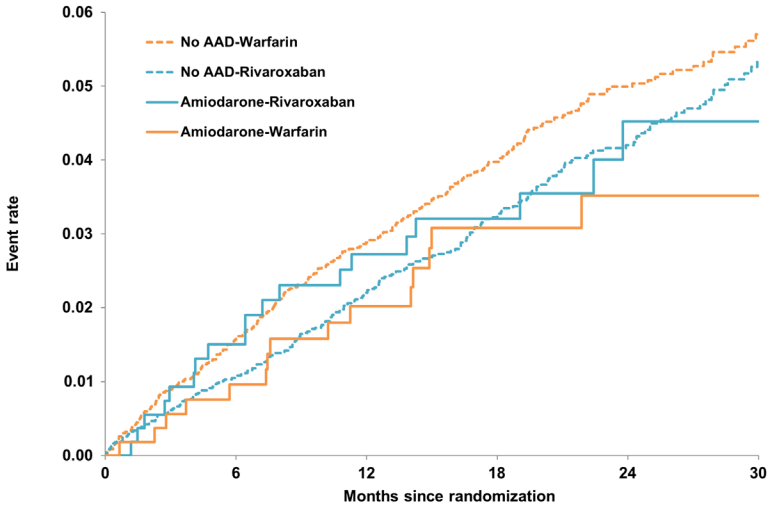
No AAD	12503	11865	11247	8201	4974	2132
Amiodarone	1132	991	904	624	359	118
Other AAD	536	464	422	305	169	69

Figure 2 Kaplan-Meier curves for all-cause mortality stratified by AAD use at baseline. P = NS for all 3 pairwise comparisons by using multivariable Cox models. AAD = antiarrhythmic drug.

we cannot confirm that 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 supratherapeutic INRs, and TTR is well known to correlate closely with both bleeding and ischemic outcomes.[7] However, despite the increased overall risk of patients receiving amiodarone and the lower TTR in these patients, our data did not show an 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 Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial and others, which suggest AADs (amiodarone in particular) increase the risk of morbidity and mortality, specifically noncardiovascular mortality.[8,9] Yet, 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 the ROCKET



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 vs warfarin, which were stratified by amiodarone use at baseline (vs no AAD). AAD = antiarrhythmic drug; CNS = central nervous system.

Table 4 Adjusted outcomes of rivaroxaban vs warfarin stratified by amiodarone use at baseline

	Amiodarone			No AAD			
Outcome	Rivaroxaban, events per 100 patient-years (total events)	Warfarin, events per 100 patient-years (total events)	Rivaroxaban vs warfarin, HR (95% CI)	Rivaroxaban, events per 100 patient-years (total events)	Warfarin, events per 100 patient-years (total events)	Rivaroxaban vs warfarin, HR (95% CI)	Interaction *P* (amiodarone and treatment)
Stroke or non-CNS embolism	2.14 (19)	1.74 (15)	1.71 (0.80–3.65)	2.16 (237)	2.54 (279)	**0.82 (0.68–0.98)**	.063
Bleeding							
Major or NMCR bleeding	15.90 (108)	13.82 (92)	1.35 (0.94–1.92)	15.00 (1284)	14.53 (1261)	**1.12 (1.00–1.25)**	.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)	.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)**	.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)**	.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)**	.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)**	.71

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

AF trial. All patients received stroke prevention therapy (eg, 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 receiving AAD therapy because 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, HRs of treatment with rivaroxaban vs 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 an increased risk of GI bleeding. However, in patients receiving amiodarone, the HRs trend the other way, suggesting an increased risk of ischemic and bleeding outcomes in patients assigned to rivaroxaban vs warfarin and a borderline *P* value for the interaction term (.06). Importantly, the interpretation of these results is limited primarily by power. Event rates in these groups are relatively low and yield wide CIs; definitive conclusions about the treatment effects cannot be drawn. This is particularly evident from the fact that the risk of fatal bleeding and risk of intracranial hemorrhage—events frequently linked—trend in opposite directions.

In addition, 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 those in patients receiving warfarin and no AAD. This discrepancy accounts for the difference in HRs between patients treated and not treated with amiodarone. However, in a detailed analysis of TTR in patients receiving warfarin, the 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. The current US Food and Drug Administration label for rivaroxaban states that patients with renal impairment taking P-glycoprotein and weak-to-moderate cytochrome P450 3A4 inhibitors (such as amiodarone) may have increased 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 Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation (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]

Study limitations

The present 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 of 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 vs warfarin. Lastly, we cannot exclude the use of amiodarone for ventricular arrhythmias.

Conclusion

A minority of patients in the ROCKET AF trial were treated with an AAD. However, AAD therapy was not associated with worse clinical outcomes in anticoagulated patients with AF. The addition of amiodarone to warfarin significantly reduces TTR, and the effect of amiodarone on rivaroxaban effectiveness requires additional investigation.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2014.03.006.

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