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Renin Angiotensin Blocker Pre-Treatment and Recurrence After Pulmonary Vein Isolation in Patients with Paroxysmal and Persistent Atrial Fibrillation.

Boaz D Rosen, MD[1,2], Nazem Akoum, MD[1], Nathan Burgon, PhD[1], Gaston Vergara, MD[1], Nassir Marrouche, MD[1] and Feras Bader, MD[1].

[1]*Department of Medicine, Cardiology Division, University of Utah, Salt Lake City, UT.* [2]*Department of Medicine, Harbor Hospital, Baltimore, MD.*

Abstract

Introduction: Pulmonary venous isolation has emerged as an effective method for preventing atrial fibrillation (AF) recurrence. Yet, recurrence is common. Angiotensin-receptor-blockers (ARBs) and angiotensin-converting-enzyme-inhibitors (ACEI) are effective in reducing the extent of myocardial remodeling and fibrosis. Our aim was to study whether pretreatment with ARBs and ACEI was effective in decreasing recurrence after pulmonary vein isolation for patients with AF.

Methods: Three hundred and twelve consecutive patients who underwent ablation from 12/2006 until 7/2010 were followed for at least one year. All patients underwent MRI before ablation to assess atrial fibrosis. Data include demographic characteristics, comorbidities, AF type and information regarding treatment with ACEI or ARBs.

Results: Most patients were men (62%), mean age was 64. Hypertension (HTN) was present in 60%. Their mean ejection fraction was 60%. There were 104 patients (33.3%) treated with ACEI, and 13.5 % were treated with ARBs prior to ablation. Ninety seven patients (31.1%) had AF recurrence. AF type was a significant predictor for recurrence (recurrence with paroxysmal, persistent and long-standing persistent: 23.75, 37.3 and 60%, respectively, p=0.005). The most important factor predicting recurrence was increased pre-ablation atrial fibrosis (p<0.0001). Recurrence was more frequent in patients treated with ACEI (40.4% vs 26.4% untreated patients, p=0.012). In the ARB treated group, 38.1% vs 30.0% untreated experienced recurrence (p=0.3). After multivariable adjustment for demographics, risk factors and atrial fibrosis, treatment with ACEI was associated with increased rate of recurrence in patients with persistent AF (hazard ratio: 2.6, p=0.003). There was no significant relation between ACEI pretreatment and recurrence in patients with paroxysmal AF (HR- 0.83, p=0.7), or between ARB pre-treatment and recurrence in patients with paroxysmal as well as persistent AF (p=0.2 and 0.53, respectively).

Conclusions: Pretreatment with ACEI or ARBs is not associated with reduced recurrence rate in patients with paroxysmal or persistent AF undergoing ablation.

Introduction

Atrial fibrillation (AF) is a common arrhythmia. The prevalence of AF increases with age, especially in patients with hypertension (HTN), coronary artery disease (CAD) and congestive heart failure (CHF).[1,2]

Pulmonary vein isolation has emerged as an effective method of treating AF. However, recurrences are frequent and range between 10-40%.[3-5] AF recurrence is dependent on multiple factors including operator experience, patient selection, AF type (paroxysmal, persistent and permanent),[6,7] coexistence of CHF and AF etiology. The extent of pre-ablation atrial scar correlates with post-ablation recurrence of AF.[8]

Renin-angiotensin aldosterone system (RAAS) has multiple effects in the pathogenesis and persistence of AF. The RAAS interacts with the adrenergic system and promotes both electrical and structural remodeling including atrial fibrosis.[9-11] Therefore, it is biologically plausible that angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEI) will be effective in preventing AF and decrease its recurrence.

Several studies sought to determine the effectiveness of treatment with ACEI and ARBs in preventing AF or reducing the risk of recurrence after cardioversion. In several meta-analyses, treatment with ACEI and ARBs was associated with 19-28% decrease in AF recurrence after cardioversion.[12-14] In general, the effect of ARBs tended to be greater than ACEI.[9,10,15-17] However, in a large double blind placebo controlled study, valsartan was not shown to decrease

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Corresponding Author:
Dr Boaz Rosen.
Department of Medicine.
Harbor Hospital, 3001
S Hanover st,
Baltimore, MD, 21225.

AF recurrence.[18]

In three retrospective studies and one prospective registry, ARB and ACEI use was not associated with decreased AF recurrence post antral pulmonary vein isolation.[10,19-22]

Only one study demonstrated a decreased recurrence of AF post ablation in patients treated with either ACEI or ARBs.[23] Despite these negative results, we believe that further information is warranted given the multiple biologic effects of ACEI and ARB.

Compared with patient with persistent AF, patients with paroxysmal atrial fibrillation tend to have less left atrium (LA) remodeling and fibrosis.[24] Therefore, it is possible that the pre-treatment with ACEI and ARBs would be more effective in patients with paroxysmal atrial fibrillation.

The aims of this study were:

1. Evaluate the efficacy of pre-treatment with ARBs and ACEIs in patients undergoing antral pulmonary vein isolation.

2. Assess whether ARB or ACEI pretreatment has differential effects in patients with paroxysmal and persistent atrial fibrillation.

Methods

Participants

We studied 312 consecutive patients who underwent AF ablation at the University of Utah Medical Center between 12/2006 and 7/2010 and were followed for at least one year after ablation.

All patients were included in the analysis, except those who were lost to follow up post ablation, or those who developed major post-ablation complications (e.g tamponade, atrio-esophageal fistula in whom the procedure was not completed). Patients in whom AF ablation deemed unsuccessful (remained in permanent AF) were not included in the analysis, since we believe that in these patients, the likelihood of a late conversion to sinus rhythm is low, and the effect of RAAS inhibitors in decreasing AF recurrence cannot not be demonstrated.

Study Design

Variables that were retrieved include: age, gender, BMI, ethnicity, presence/ absence of CHF and CAD, type of AF (paroxysmal, persistent and long standing persistent), history of HTN, diabetes mellitus (DM) and smoking. Information regarding treatment with ACEI and/or ARBs as well as spironolactone prior to the ablation procedure was obtained as well. The rate of AF recurrence post ablation was studied. In addition, the time to the first post ablation recurrence was determined (time is measured from the date of ablation procedure).

Paroxysmal AF was defined as AF that terminates spontaneously within less than seven days. Persistent AF terminates after more than 7 days or by pharmacological therapy or DC cardioversion. Long standing persistent atrial fibrillation lasts continuously longer than one year.[25]

Prior to AF ablation all patients underwent delayed enhancement cardiac MRI to determine the extent of atrial fibrosis (see below).[24] The effect of atrial fibrosis on the rate of recurrence in patients treated/ not treated with ACEI or ARB was also determined. Institutional review board approval was obtained.

Pulmonary vein isolation and atrial debulking and follow up. All patients underwent pulmonary vein isolation, posterior left atrial wall and septal debulking as described previously.[24,26] During the procedure IV isoproterenol was given routinely to reveal AF or other supraventricular tachyarrhythmias.

Prior to ablation all patients were anticoagulated with warfarin (target INR 2-3). Post ablation, unless contra-indicated, the patients continued with warfarin for at least 3 months. Patients in whom atrial fibrillation was documented continued warfarin. After the procedure, all patients carried an event monitor for 60 days to detect AF recurrence or other arrhythmias. Three weeks after completing event monitoring, all patients underwent an eight day Holter monitoring. Documented AF run longer than 30 seconds is defined as AF recurrence. Anti-arrhythmic medications are typically discontinued after AF ablation unless AF or other arrhythmias were detected. Treatment with ACEI and ARB was continued after the procedure without interruption, unless contra-indicated.

The first three months after AF ablation were considered a `blanking period`. During this time frame, AF recurrence was not considered an ablation failure.

DE-MRI Acquisition and quantification of atrial scar. The patients underwent MRI scanning in a 1.5-T Avanto clinical scanner (Siemens Medical Solutions, Erlangen, Germany) using a phased-array receiver coil. To determine the extent of myocardial fibrosis, the patients received IV Gadolinium (0.1 mmol/kg body weight; Multihance, Braco Diagnostic Inc, Princeton, NJ). DE-MRI were acquired 15 minutes after contrast injection using 3-dimensional (3-D) inversion-recovery, ECG gated, gradient-echo pulse sequence with fat saturation. The images were acquired during free breathing using respiration navigation.

Typical Acquisition Parameters

Voxel size of 1.25 X 1.25 X 2.5 mm, flip angle 22°, TR/ TE were 6.1/2.4 ms, inversion recovery time was 230 to 320 ms, and parallel imaging with GRAPPA technique with R=2 and 42 reference lines. EKG gating was used to acquire phase-encoding views during diastole. Scan time for DE images was 5 to 9 minutes. 16-22 slices were acquired. Additional details were previously described by McGann and Oakes.[24,26]

Analysis was done using DICOM images, processed with OsiriX for visualization. Quantification of the images was done using Matlab software (Mathworks, Inc., Natick, Massachusetts). Lesions in each slice were quantified using volume rendering. Percentage lesion volume was determined by the ratio of the sum of the lesion volumes in all slices divided by the left atrial wall volume.

Statisticak Analysis:

The association between pretreatment with ARB or ACEI or any of them and recurrence of AF was tested using $\chi 2$ test or Fisher exact test when appropriate. Unadjusted differences between continuous variables were studied using ANOVA or Wilcoxon rank sum test when appropriate.

Time to first recurrence was studied in pre-defined groups (no prior treatment/ treatment with ARB or ACEI) using Kaplan-Meier analysis. Cox models were used to test whether pretreatment with ACEI, ARB or any of them predicted AF recurrence after ablation. Variables entered in Cox model included recurrence, time of recurrence, demographic parameters (age, gender), presence of CAD, CHF, HTN, DM, extent of pre-ablation atrial fibrosis (Utah classification- Class I: LA fibrosis ≤ 5%; Class II: >5% to ≤ 20%; Class III: >20% to ≤ 35%; Class IV: >35%),[27] and pretreatment with ACEI and ARB. Patients with paroxysmal and persistent AF were studied separately.

Data are presented as mean ±SD. Differences are considered significant if p<0.05. Analyses were done using STATA-8 software (Stata Inc., College Station, Texas).

Results

There were 312 consecutive patients included in the analysis. Their demographic and clinical characteristics are shown in Table 1. Most patients were men (62%) and their mean age was 64±12 years. Sixty percent of the patients had HTN, and CAD was present in 14% of patients. Only 9% had a history of CHF. Their mean LVEF was 60±11% and the mean extent of pre-ablation atrial fibrosis was 17±12%. After ablation, AF recurred in 31% of patients. Mean and median times of recurrence were 228±199, and 135 days after the ablation procedure, respectively.

Medications

Table 1: Demographic and clinical characteristics (mean± S.D).

Parameter (n=312)	Value
Age	64±12
Men (%)	194 (62)
Weight (kg)	88±21
BMI (kg/m2)	29±6
Type of atrial fibrillation (%)	
Paroxysmal	51
Persistent	46
Permanent	3
Hx of CAD (%)	43(14)
s/p MI (%)	14(4)
CHF (%)	28(9)
DM (%)	48(15)
HTN (%)	188(60)
Hx of Smoking (%)	62(20)
Hx of Stroke (%)	32 (10)
CABG(%)	18(6)
Valvular surgery (%)	7(2)
ICD/ Pacemaker (%)	24(8)
EF (%)	60±11
Pre-ablation fibrosis	17±12
Severity of fibrosis (Utah stage)	
1	19(6)
2	196 (63)
3	71(23)
4	26(8)
Treatment (%)	
Anti-arrhythmic drugs (%)	57(18)
Class I	31(63)
Class III	21(37)
Any RAAS inhibitor.	140(45)
ACE Inhibitors	104(33)
ARB	42(13)
Spironolactone	17 (5)
Statins	136(44)
Recurrence (%)	97(31)
Time of recurrence (days)	228±199

Abbreviations: CAD- coronary artery disease, MI- myocardial infarction, CABG- coronary artery bypass graft, CHF- congestive heart failure. DM- diabetes mellitus, HTN- hypertension, ICD- implantable cardioverter- defibrillator, EF- ejection, fraction. RAAS- renin –angiotensin-aldosterone.

Table 2: Demographic and clinical characteristics of treated and untreated patients (RAAS)*

Characteristics	RAAS inhibitors		Significance
	Treated 140 (45)	Untreated172 (55)	
Age	66±11	62±13	0.008
Gender			
men	103 (53)	91 (47)	
women	69 (59)	49 (41)	0.35
BMI (kg/m2)	31±7	28±6	0.0003
EF (%)	60±11	60±11	0.76
Pre-ablation fibrosis (%)	17±12	17±12	0.82
CAD			
yes	27 (63)	16 (37)	
no	113 (42)	156 (58)	0.011
HTN			
yes	113 (60)	75 (40)	
no	27 (22)	97 (78)	<0.001
CHF			
yes	20 (71)	8 (29)	
no	120 (42)	164(58)	0.003
DM			
yes	35 (73)	13 (27)	
no	105 (40)	159 (60)	<0.001

* Values are given as mean±standard deviation. Numbers in parentheses indicate percentage. Significance for continuous variables was tested using t-test, and for categorical variables using χ2. Abbreviations- see Table 1.

Due to their co-morbidities including HTN, CAD and CHF, a considerable number of the study patients received medications including statins (44%) and RAAS antagonists (45%). Of the entire cohort, 104 (33%) patients were treated by ACEI and 13% received ARBs (Tables 1 and 2). Only 17 patients (5%) were treated with spironolactone. Prior to ablation 18% of the patients received anti-arrhythmic drugs.

Patients treated with ARBs and ACEI were older, and more likely to have CHF, HTN and DM. There was no difference in the severity of atrial fibrosis between patients treated and not treated with RAAS inhibitors.

Factors Predicting Recurrence (Table 3)

Patients older than 65 (median age) tended to have a higher rate of AF recurrence than younger individuals (36% vs 25%, P=0.031). A history of DM was associated with a greater rate of recurrence (p<0.001), while patients with history of HTN tended to have more recurrences (p=0.059). Prior history of CHF (p=0.58) as well as CAD (p=0.19) were not associated with AF recurrence.

Patients with a history of paroxysmal AF had lower recurrence rates compared with those with persistent and long standing persistent AF (p=0.005). The strongest predictor of AF recurrence was extent of pre-ablation atrial fibrosis. Atrial fibrosis in patients who had AF recurrence was significantly greater than the extent of fibrosis in patients who did not experience AF recurrence (23.3±15.4 vs 14.1±8.5, p<0.0001).

Association between RAAS blockers and AF recurrence in patients with paroxysmal and persistent AF (Tables 4 and 5).

Previous treatment with ACEI was associated with increased recurrence rate after AF ablation (40% vs 26%, p=0.012). Results did not change after multivariable adjustment (Hazard ratio 1.62, p=0.042).

There was no significant difference in the rate of AF recurrence

Table 3: Factors associated with recurrence of atrial fibrillation

Parameter	Recurrence		P value for significance*
Age>65	<65: 36/144 (25)	>65: 61/168 (36)	0.031
Gender	Male: 58/194(30)	Female: 39/118 (33)	0.56
	Risk factor present	Risk factor absent	
Hx of Hypertension	66/188 (35)	31/124(25)	0.059
Hx of CHF	10/28(36)	87/284(31)	0.58
Hx of DM	26/48(54)	71/264(27)	<0.001
Hx of Smoking	23/62 (37)	74/250 (30)	0.25
Hx of CAD	17/43(40)	80/269(30)	0.19
EF	<55%: 22/63 (35)	≥55%: 75/249(30)	0.46
Type of AF	Paroxysmal Persistent Long standing Persistent	38/160 (24) 53/142 (37) 6/10 (60)	0.005
Extent of pre-ablation atrial fibrosis	Recurrence: Non-recurrence:	23.3±15.4 14.1±8.5	<0.0001

* Significant differences between categorical variables was tested using Fisher exact test. Significant differences between continuous variables (extent of pre-ablation fibrosis) was tested using the Wilcoxon rank sum test. Abbreviations see Table 1.

in patients who had been treated with ARB compared to untreated patients (38% vs 30%, respectively, p=0.29, and after adjustment, p=0.80). Only six patients were treated with both ACEI and ARBs precluding analysis of combination therapy efficacy.

Patients pre-treated with ACEI with paroxysmal AF had similar rates of recurrence compared with untreated patients (25% vs 23%, respectively, p=0.82). In contrast, patients with persistent AF who were pre-treated with ACEI had significantly higher recurrence rates than untreated patients (54% vs 27%, p=0.001). These results did not change after adjustment (Hazard ratio- 2.58, p=0.003).

Patients with paroxysmal AF pretreated with ARBs had a higher recurrence rate compared to untreated patients (45% vs 21% res, p=0.017). However, this difference diminished after multivariable adjustment (p=0.19). In contrast, there was no difference in recurrence rates in ARB treated patients with persistent AF compared to untreated patients (p=0.56).

In order to study whether RAAS treatment is effective in patients with different degrees of left atrial fibrosis, subgroup analysis was performed. Treatment with ACEI was not associated with decreased AF recurrence even in patients with a mild degree of fibrosis (<15.25%). There was no effect of ARB treatment on the rate of recurrence in any of the groups (data not shown).

Time to AF recurrence (Fig 1). As shown in Fig 1A, the time to first recurrence was shorter in patients treated with ACEI compared to untreated patients. In contrast, time to first recurrence was similar in patients treated and untreated with ARBs (p=0.22), (Fig 1b).

Discussion

The Main Findings of Our Study are:

1. Pre-treatment with RAAS including ACEI, ARBs was not associated with significant reduction of AF recurrence after AF ablation.

2. Time to first AF recurrence was similar in ARB treated and untreated AF patients.

3. Lack of beneficial effect in of RAAS was evident both in patients with paroxysmal or persistent AF. Patients with persistent AF who were treated with ACEI tended to have more recurrence than untreated patients.

Recurrence of AF after ablation was associated with several pre-existing conditions including HTN and DM. As has been reported earlier based on the same cohort, the extent of pre-ablation atrial fibrosis detected by contrast enhanced MRI was associated with increased AF recurrence.[8,24] Yet, pretreatment with RAAS inhibitors did not prevent AF recurrence in patients probably because of the severity of atrial fibrosis.

Treatment with ACEI as well as ARB and spironolactone was reported to be effective in decreasing cardiovascular morbidity and mortality in patients with LV systolic dysfunction.[28-34] A large meta-analysis that included 11 studies and total of 56,308 participants showed that treatment with ACEI and ARBs was effective in preventing the development of AF in patients with LV systolic dysfunction and LV hypertrophy.[13]

Other data indicate that ACEI and ARBs are effective in decreasing AF recurrence after DC cardioversion in addition to anti-arrhythmic drugs.[9,16,17,35,36] Yet, a recent large randomized placebo controlled study did not show a decrease in the recurrence of AF.18 Candesartan was found to decrease the extent of atrial fibrosis in dogs with AF induced by rapid atrial pacing.[10]

The question whether RAAS inhibitors decrease AF recurrence in patients after AF ablation is an important one. Antral pulmonary vein isolation is an effective technique for treating AF. Yet, a significant number of patients, between 10-40% experience recurrence of AF.[3,5,36] In the current study, recurrence rate was 31%.

It has been shown that short term recurrence rate correlated inversely with the extent of atrial tissue injury induced by the ablation procedure. An increased scar formation after ablation was associated with a lower rate of AF recurrence.[26]

Few studies addressed the effect of ACEI and ARBs in preventing AF recurrence after ablation. In four studies, ARBs and ACEI were not effective in preventing AF recurrence after pulmonary venous isolation.[4,19-21] In contrast, one study showed that treatment with ACEI and ARBs was associated with decrease in AF recurrence post ablation.[23]

There are several possible causes for the negative results of the study. It is possible that in these patients, both structural and electrical atrial remodeling, especially fibrosis were advanced, and at this stage, RAAS inhibition or statin therapy would not be effective. In this regard, it would have been expected that ACEI, ARBs or spironolactone would have been more effective in patients with a reduced extent of atrial fibrosis. This study is retrospective and the patients that were treated with RAAS inhibitors or statins were not randomly assigned

Table 4: Use of medications and risk of recurrence*

Medication	Recurrence rate		p value for sig *	Multivariable adjustment §
	With med	Without med		
ACEI	42/104 (40)	55/208 (26)	0.012	HR: 1.62, (95%CI: 1.02, 2.59, p=0.042)
ARB	16/42 (38)	81/270 (30)	0.29	HR: 1.08, (95%CI: 0.60, 1.95, P=0.80)
ACEI or ARB	54/140 (39)	43/172 (25)	0.01	HR: 1.58, (95%CI: 1.05, 2.39, p=0.028)

* Significance was tested using χ2

§ Cox models. Variables entered in the model include: age, gender, history of HTN, DM, CHF, CAD and the extent of pre-ablation atrial delayed enhancement defined by Utah Classification. HR- Hazard ratio, (95% confidence interval, P value).

Table 5: Recurrence in patients with paroxysmal and persistent AF: RAAS treated versus untreated patients.

Treatment		AF recurrence in RAAS inhibitors treated vs ntreated patients			Multivariable adjustment	
		Treated†	Not treated	p	Hazard ratio§	P
ACE-inhibitors	Paroxysmal	11/44(25)	27/116(23)	0.82	0.83 (95%CI: 0.32, 2.15)	0.70
	Persistent	30/56 (54)	23/86 (27)	0.001	2.58 (95%CI: 1.40, 4.78)	0.003
ARBs	Paroxysmal	9/20 (45)	29/140(21)	0.017	1.97 (95%CI: 0.71, 5.48)	0.19
	Persistent	7/22(32)	46/120(38)	0.56	0.77 (95%CI: 0.34, 1.74)	0.53
RAAS	Paroxysmal	19/63(30)	19/97(20)	0.13	1.39 (95%CI: 0.59, 3.26)	0.45
	Persistent	34/73(47)	19/69(28)	0.019	1.89 (95%CI: 1.11,3.22)	0.02

Abbrev: RAAS- renin-angiotensin aldosterone inhibitors.
† percentage. § Cox models. Variables entered in the model include: age, gender, history of HTN, DM, CHF, CAD and the extent of pre-ablation atrial delayed enhancement defined by Utah Classification. HR- Hazard ratio, (95% confidence interval, P value).

to therapy, and more likely had other underlying disorders including CAD, CHF, HTN or DM. Although these factors were adjusted in the multivariable logistic regression analysis, it is a possible that other important underlying conditions or confounding variables were not considered.

A third possibility is that patients after AF ablation constitute a specific group that may not necessarily benefit from treatment with ARB/ACEI and spironolactone. Although pre-ablation atrial fibrosis an important risk factor of recurrence after AF ablation, it has been shown that increased post ablation atrial injury and scarring shown by delayed hyperenhancement is associated with decreased extent of AF recurrence.[26] Therefore, there is a possibility that despite their hemodynamic effect and sympathetic modulation, they would be less effective because of their anti-fibrotic effect post AF ablation. This is a theoretical consideration that warrants further testing.

Despite the negative results of this analysis, it is important to emphasize that RAAS inhibitors as well as statins have a well-established evidence based role in the treatment of CAD, CHF, HTN and diabetes mellitus. Their lack of effect on post ablation AF recurrence should not preclude patients from receiving these important medications.

Finally, the seemingly contradictory effects of ARB vs ACEI in patients with paroxysmal and persistent AF (i.e no association in patients with paroxysmal AF and increased recurrence in patients with persistent AF treated with ACEI, and opposing effect with ARBs, see Table 5) were unexpected and hard to explain. The most likely explanation is that it is statistical variation. In addition, it is possible that there were confounding variables unaccounted for. We do not believe that these findings are due to differences in the pharmacologic activity of ARBs and ACEI`s.

Limitations

Our study includes a large number of patients (n=312), all of whom were followed for at least one year. This is a retrospective analysis, and the patients who received ACEI/ ARB and spironolactone may have had other co-morbidities compared to those who were not treated with these medications. The number of patient treated with combination of ACEI and ARBs or with spironolactone was small, precluding analysis of the efficacy of such treatments. The effect of RAAS inhibitors in reducing AF recurrence should be further tested by a randomized placebo controlled trial. In addition, the exact time-length of treatment with ARB, ACEI, spironolactone prior to ablation could not be ascertained. Finally, the analysis was limited to one year recurrence.

Conclusions:

Treatment with angiotensin converting enzyme inhibitors, antiotensin receptor blockers or aldosterone antagonists prior to AF ablation was not effective in decreasing the rate of recurrence post ablation. There were no subgroups of patients, including patients with paroxysmal or persistent AF or varying extent of atrial fibrosis in whom treatment with RAAS inhibitors or statins was found to be beneficial.

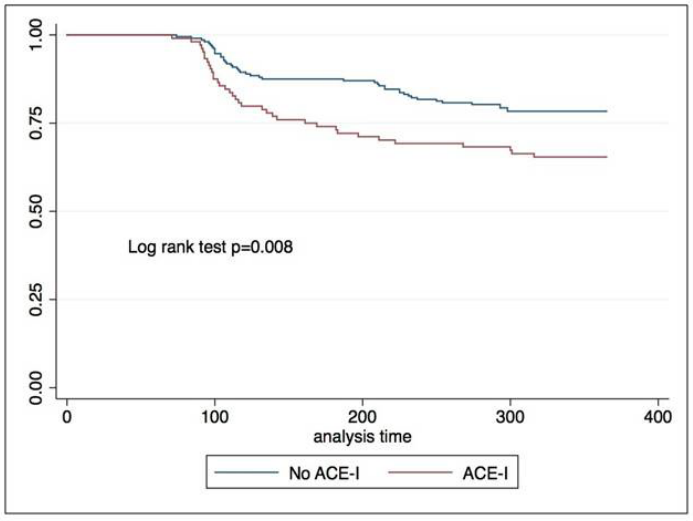

Figure 1A: Time to recurrence of AF in patients treated with ACE inhibitors and ARBs.

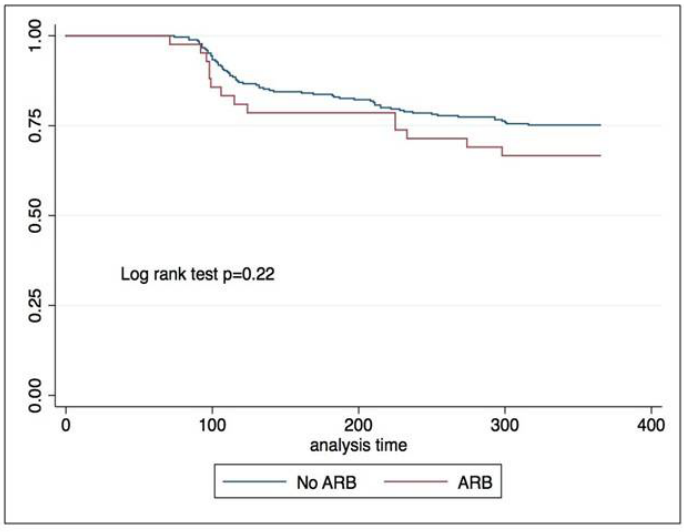

Figure 1B: Time to recurrence of AF in patients treated with ACE inhibitors compared to untreated patients.

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