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Effect of Angiotensin Converting Enzyme Inhibitors and Receptor Blockers on Appropriate Implantable Cardiac Defibrillator Shock in Patients with Severe Systolic Heart Failure (From the GRADE Multicenter Study)

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Abstract

Sudden cardiac death (SCD) is a leading cause of mortality in patients with cardiomyopathy. While angiotensin converting enzyme inhibitors (ACEi) and receptor blockers (ARB) decrease cardiac mortality in these cohorts, their role in preventing SCD has not been well established. We sought to determine whether the use of ACEi or ARB in patients with cardiomyopathy is

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associated with a lower incidence of appropriate implantable cardiac defibrillator (ICD) shocks in the Genetic Risk Assessment of Defibrillator Events (GRADE) study which included subjects with an ejection fraction of ≤30% and ICDs. Treatment with ACEi/ARB versus no ACEi/ARB was physician dependent. There were 1509 patients (mean age [SD] 63[12] years, 80% male, mean [SD] EF 21% [6%]) with 1213 (80%) on ACEi/ARB, and 296 (20%) not on ACEi/ARB. We identified 574 propensity matched patients (287 in each group). After a mean (SD) of 2.5(1.9) years, there were 334 (22%) appropriate shocks in the entire cohort. The use of ACEi/ARB was associated with lower incidence of shocks at 1, 3 and 5 years in the matched cohort (7.7%, 16.7%, 18.5% vs. 13.2%, 27.5%, and 32.0% (RR= 0.61[0.43–0.86], p =0.005). Among patients with GFR >60 and 30–60 ml/min/1.73m^2, those on no-ACEi/ARB were at 45% and 77% increased risk of ICD shock as compared to those on ACEi/ARB, respectively. ACEi/ARB were associated with significant lower incidence of appropriate ICD shock in patients with cardiomyopathy and GFR ≥30 ml/min/1.73m^2, and with neutral effect among those GFR <30 ml/min/1.73m^2.

Keywords

ACEi/ARB; cardiomyopathy; appropriate ICD shock

Introduction

Sudden cardiac death (SCD) is a leading cause of cardiovascular mortality in patients with left ventricular (LV) systolic dysfunction[1]. Angiotensin converting enzyme inhibitors (ACEi) and receptor blockers (ARB) antagonize the action of angiotensin II, a known precursor of interstitial fibrosis[2, 3] that is associated with ventricular arrhythmia[4–8]. While ACEi/ARB decrease cardiac mortality in LV dysfunction patients[9–11], their role in preventing SCD has not been well established. In one study, Obeyesekere et al. showed that absence of ACEi/ARB therapy was a predictor of appropriate ICD shock; however, the study was of small sample size, limited events, and excluded patients in the secondary prevention population[12]. Hence, the aim of the study is to explore the role of ACEi/ARB in predicting appropriate implantable cardiac defibrillator (ICD) shocks in a large multicenter registry of patients with severe systolic dysfunction. We hypothesized that ACEi/ARB usage is associated with a decreased incidence of appropriate shock in patients with cardiomyopathy. We also sought to elucidate the role of ACEi/ARB in predicting appropriate ICD shocks in a) distinct glomerular filtration rate (GFR) strata, b) in ischemic versus non-ischemic cardiomyopathy, and lastly c) based on indication for ICD implantation cohorts (primary versus secondary prevention).

Methods

Subjects included in this study are from the NHLBI sponsored prospective observational multi-center GRADE (The Genetic Risk Assessment of Defibrillator Events) study, designed to identify genetic modifiers of arrhythmic risk[13]. Inclusion criteria were: patients who were ≥18 years of age with a diagnosis of at least moderate systolic left ventricular dysfunction (EF ≤30%), and who had an ICD at the University of Pittsburgh Medical Center (coordinating center; Pittsburgh, PA), Emory University Medical Center, (Atlanta, GA),

Massachusetts General Hospital, (Boston, MA), Ohio State University Medical Center, (Columbus, OH), Mid-Ohio Cardiology (Columbus, OH) or the Pittsburgh Veterans Affairs Medical Center (Pittsburgh, PA). Subjects were excluded if they had intractable Class IV heart failure, and conditions (other than HF) that were expected to limit survival to less than 6 months. The institutional review boards of participating medical centers approved the study and each patient gave written informed consent prior to participation. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and the trial was registered at www.clinicaltrials.gov (NCT 02045043).

A total of 1808 GRADE patients, enrolled between March 2002 and July 2010 within 5 years of ICD implantation, were considered for the current analysis. Of these, 252 patients with no available follow-up data on first appropriate shock outcome and 47 patients without ACEi/ARB medication use data were excluded. The final study population consisted of 1509 subjects and was divided to two primary comparison groups: 1213 ACEi/ARB (80%) and 296 No-ACEi/ARB (20%). Baseline measurements recorded at the first visit included demographic characteristics, left ventricular EF (by echocardiography, nuclear study, or left ventriculogram), New York Heart Association functional class, medication profile, serum electrolytes, electrocardiographic parameters, echocardiographic parameters, hemodynamic measurements, model and settings of the ICD, etiology of heart failure (ischemic versus non ischemic), and indication for device (primary versus secondary prevention). The left ventricular EF was determined by 2-dimensional echocardiography in the majority of subjects.

Ischemic HF patients included those with a documented history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or ≥50% diameter stenosis of any of the 3 major coronary epicardial arteries.

Duration of follow-up was defined as the interval from the date of enrollment or ICD implantation (whichever came later) to the date of the first endpoint or last follow-up when the data were censored. Clinical follow-up was done yearly by telephone by the research coordinator and ICD interrogation was performed. ICD shocks, implantation of ventricular assist device, heart transplantation and mortality data were collected and the validity of these data ascertained by ICD interrogation and hospital medical record documentation. ICD telemetry from all device downloads was sent to the coordinating center for review. Appropriate ICD shocks were adjudicated by two cardiologists, and a third in cases of disagreement. ICD programming was left to the discretion of the local electrophysiologist to select the cutoff rate for fast ventricular tachycardia (VT) and ventricular fibrillation (VF). Shocks for supraventricular tachycardia (SVT) were excluded from analyses. Episodes that only required anti-tachycardia pacing (ATP) were excluded from analyses. Episodes that required both ATP and appropriate ICD shocks were included.

The primary endpoint in this study was time to first appropriate ICD shock for ventricular tachycardia or ventricular fibrillation. Secondary endpoints included all-cause death, and the composite endpoint of death, ventricular assist device or cardiac transplantation.

Patients with missing appropriate ICD shock follow-up or discharge ACEi/ARB status were excluded from the study. A total of 25 other patient factors (Table 1) were considered in this analysis and 669 of 1509 study patients had 100% complete data (44%). Only 5 patient factors (QRS interval, QT_C interval, systolic Blood Pressure, body mass index, and creatinine) had missing data in more than 5%. Data on medical history and medications intake were imputed assuming normal condition and no medication, respectively. Missing values were imputed using the median or the mode of the variable as applicable. Few patients had missing GFR levels and they were categorized as having normal GFR (> 60 ml/min/1.73 m^2). There was no difference in results when missing GFR data were excluded and only unimputed data were used.

The ACEi/ARB and No-ACEi/ARB patient groups exhibited significant differences in demographic and risk factors (Table 1) that may confound any association between the outcome (development of appropriate shock after ICD insertion) and ACEi/ARB medication intake. To minimize such confounding, we used propensity score matching to derive matched sub-cohorts of equal size. No-ACEi/ARB propensity score was derived via a non-parsimonious logistic multivariate regression model that considered No-ACEi/ARB as the dependent outcome variable. A total of 25 risk factors (identified from prior published trials and existing literature) were entered into the model. The resulting propensity scores were distinctly different for ACEi/ARB (Yes) versus ACEi/ARB (No) patients (mean [SD]: 0.813[0.079] vs. 0.768[0.097] respectively; p<.001]. The corresponding C-statistic values (area under the ROC curve) was 0.64±0.02 indicating fair-to-moderate discrimination. We obtained 1-to-1 matched cohorts where a given ACEi/ARB was always matched to the closest available No-ACEi/ARB counterpart to within ±1% difference. Adequacy of patient group matching was assessed by calculating the standardized difference, d(%), separately for each factor and based on whether they were continuous or categorical as previously published[14].

Continuous data were expressed as mean (standard deviation) and categorical data were expressed as counts and percentages. Univariate comparisons were done with chi-square (X^2) for categorical factors, while continuous factors were compared by independent t-test or Mann Whitney rank sum test based on normality. Survival comparisons were done via Kaplan-Meier analysis (Log rank test). The corresponding hazard ratios (95% confidence interval) were derived by proportional hazard Cox regression analysis.

Here, to control for potential interaction between ACEi/ARB medication and kidney function, a composite variable of 6 categories was developed as follows: (1) ACEi/ARB (yes), GFR:>60 ml/min/1.73m^2, (2) ACEi/ARB (yes), GFR:30–60 ml/min/1.73m^2 (3) ACEi/ARB (yes), GFR:<30 ml/min/1.73m^2, (4) ACEi/ARB (no), GFR:>60 ml/min/1.73m^2, (5) ACEi/ARB (no), GFR:30–60 ml/min/1.73m^2, and (6) ACEi/ARB (no), GFR:<30 ml/min/1.73m^2. A p<0.05 was used to indicate significance. Analyses were done using SPSS version 21.0 software (IBM, Armonk, NY).

Results

There were 1509 patients (mean age [SD]: 63[12] years, 80% male) with 1213 (80%) on ACEi and/or ARB after enrollment. Compared to ACEi/ARB patients, the patients not on ACEi/ARB (N=296, 20%) had worse kidney function, more advanced heart failure symptoms, and were less likely to be taking digoxin while other patient factors were similar (Table 1). After propensity matching, there were 287 patients in each group that were well matched (Table 1).

At a mean (SD) follow-up of 2.5(1.9) years, a total of 334 patients had experienced one or more appropriate shock (22%) in the entire study population. Patients who had an appropriate shock had more co-morbidities and were less likely to be on ACEi/ARB (Table 2).

The 1, 3 and 5 years incidence of ICD shock in the matched cohort were 7.7%, 17%, 19% for patients on ACEi/ARB vs. 13%, 28%, and 32% for patients on no-ACEi/ARB (RR=0.61[0.43–0.86], p =0.005; Figure 1). On multivariate analysis, independent predictors of ICD shock included no-ACEi/ARB, lower GFR, younger age, reduced ejection fraction, wider QRS duration, and ischemic etiology (Table 3). The use of beta-blockers and biventricular pacing were not independent predictors of outcomes (p-value >0.2), and forcing them as factors in the multivariate model did not significantly alter the findings.

Patients with lower GFR were more likely to have received an ICD shock (Supplement figure 1/efigure 1). When stratified to GFR categories, the use of ACEi/ARB was associated with significantly fewer shocks for patients with GFR >60 ml/min/1.73m^2 and with a trend for those with GFR 30–60 ml/min/1.73m^2, but was not significant for those with GFR <30 ml/min/1.73m^2 (Figure 2). There was a significant interaction between ACEi/ARB and GFR (p =0.046 in the matched cohorts). Among patients with normal GFR, those on no-ACEi/ARB were at 45% increased risk of ICD shock as compared to those on ACEi/ARB (Table 3). Similarly, patients with GFR 30–60 ml/min/1.73m2 on no-ACEi/ARB had more than 77% increased risk in shock as compared to those on ACEi/ARB (HR 2.05 [1.32–3.16] vs. 1.28 [0.96–1.69]). Those with GFR <30 ml/min/1.73m^2 had the worst outcome irrespective of the use of ACEi/ARB (Table 3).

Furthermore, ACEi/ARB were associated with lower incidence of appropriate ICD shocks among patients with ischemic cardiomyopathy (matched cohort), but not among those with non-ischemic etiology, although the magnitude of the risk reduction was similar and with smaller number of non-ischemic patients (Figure 3).

Patients receiving ICD for secondary prevention had significant more shocks as compared to those for primary prevention (Supplement figure 1/efigure 1). The use of ACEi/ARB was associated with lower incidence of appropriate ICD shocks in the secondary prevention group and with a trend in the primary prevention group (Figure 4).

At the end of study follow-up, there were 388 total deaths (26%) and 479 (32%) subjects who reached the combined endpoint of death, transplant or ventricular assist device. In the matched cohorts, patients on ACEi/ARB had significantly lower mortality rate as compared

to those without ACEi/ARB (23% vs. 29%, HR 0.74 [0.53–1.02], p =0.07), and similarly lower combined secondary endpoint with ACEi/ARB (27% vs. 34%, HR 0.75 [0.55–1.01], p=0.06). Patients who received any appropriate ICD shock during the follow-up period had significantly higher mortality as compared to those who did not (37% vs. 23%, p <0.001), and similarly for the combined endpoint. There was significant interaction between ACEi/ARB and GFR (p<0.001 for both secondary outcomes). On multivariate analysis, patients receiving ACEi/ARB and with normal GFR had lowest mortality, while those not receiving ACEi/ARB and/or with chronic kidney disease had worse outcome (supplement table1). Patients with GFR <30 ml/min/1.73m^2 had highest mortality and secondary endpoint irrespective of the use of ACEi/ARB. Similar results were found for combined endpoint of death, transplant and ventricular assist device (supplement table 2).

Discussion

In our large cohort of subjects with severe cardiomyopathy and heart failure, we found that ACEi/ARB use is associated with significant lower incidence of appropriate ICD shocks in patients with normal or mild to moderate decrease in GFR. The results were most significant for patients with ischemic cardiomyopathy, those receiving the ICD for secondary prevention, and GFR ≥30ml/min/1.73m^2; there was also a trend for lower ICD shock for patients receiving ACEi/ARB therapy with non-ischemic cardiomyopathy and device placement for primary prevention. Patients with GFR <30 ml/min/1.73m^2 had the highest arrhythmic risk irrespective of the use of ACEi/ARB.

ACEi/ARB decrease cardiovascular mortality and all-cause mortality in patients with CHF, in post-MI patients with or without LV dysfunction, and also in patients with stable CAD. Several studies and secondary analyses of high risk patients and those with severe ischemic cardiomyopathy, showed significant 30–35% reduction in the risk of SCD, VT/VF or arrhythmic death with the use of ACEi[15,16,17, 18, 19], while others showed no significant benefit[20, 21]. On the other hand, the absence of ACEi/ARB therapy was shown to be a predictor of appropriate ICD shock in a small study with limited events of 126 patients who had an ICD placed for primary prevention for severe cardiomyopathy[12].

The reduction of ICD shock could be secondary to the role of ACEi/ARB in reducing interstitial fibrosis and scar formation. Indeed, recent studies showed that ACEi increases Connexin-43 (Cx43) levels in cardiomyopathy, a potential link for the effect seen[22, 23]. Also, ACEi/ARB prevent left ventricular remodeling, reduce concentrations of circulating angiotensin II and noradrenaline, increase baroreflex sensitivity and vagal tone, which might explain the relatively greater incidence of appropriate shocks in patients who were on no inhibitors of the renin-angiotensin system compared to patients to those who were.

We considered a number of potential subgroups including those with ischemic versus non-ischemic cardiomyopathy, renal dysfunction, and indication for device implantation. We found that patients with ischemic cardiomyopathy had more benefit if taking ACEi/ARB as compared to the non-ischemic subgroup (although the trend was present in the latter group), which could be partly related to larger scar burden[24]. Myocardial scarring however, is also seen in non-ischemic cardiomyopathy[25], and may explain the trend we have.

When we pursued stratification by GFR, patients with lower GFR had more ICD shocks which is consistent with the literature reporting chronic kidney disease as an independent predictor of ICD shock[26]. The use of ACEi/ARB therapy, however, resulted in less ICD shock among patients with preserved and mild or moderate impairment in GFR but with neutral effect among those with GFR <30 ml/min/m^2. Only 67 patients had eGFR < 30 ml/min/m^2, so the absence of an association in this group likely is a reflection of inadequate statistical power. The lower incidence of appropriate ICD shocks from ACEi/ARB is not merely due to afterload reduction. Indeed, we did adjust for the use of other afterload reducing agents that are commonly used in HF when ACEi/ARB are contraindicated such as hydralazine and nitrates, and similarly for systolic blood pressure to account for afterload effect; there was no significant change in the overall results.

Recent data from the MADIT-CRT showed that the use of β-blockers is associated with less inappropriate ICD shocks and with preferential effect (carvedilol better than metoprolol)[27]. In fact, carvedilol was associated with a 36% lower rate of inappropriate ATP and shock therapy compared with metoprolol. However, the use of β-blockers was not predictive of appropriate ICD shocks in our cohort.

Strengths of our study include the large sample size, multicenter nature, and propensity matching. Yet, it is important to acknowledge several potential limitations. First, appropriate ICD shock is not a surrogate for SCD, but remains an important endpoint as ICD shocks are associated with quality of life, syncope and SCD. Second, ventricular tachycardia and fibrillation detection rates and number of patients programmed with anti-tachycardia pacing as initial therapy (both measures are important factors in reducing ICD shocks), were not available. Third, there were few missing values, particularly GFR, QRS and QTc that had to be imputed; however, running the analysis with and without the imputed values did not alter our results (Supplement Figure 2/efigure 2). We have assessed the use of ACEi/ARB at one time only; however, we could not account for the dose of the medication, duration of being on the medication, time of discontinuation if any, and the fact that some patients who were not on ACEi/ARB could have been placed on it during one of the follow-up visits. Finally, additional useful parameters such as brain natriuretic peptide and low-density lipoprotein levels were not available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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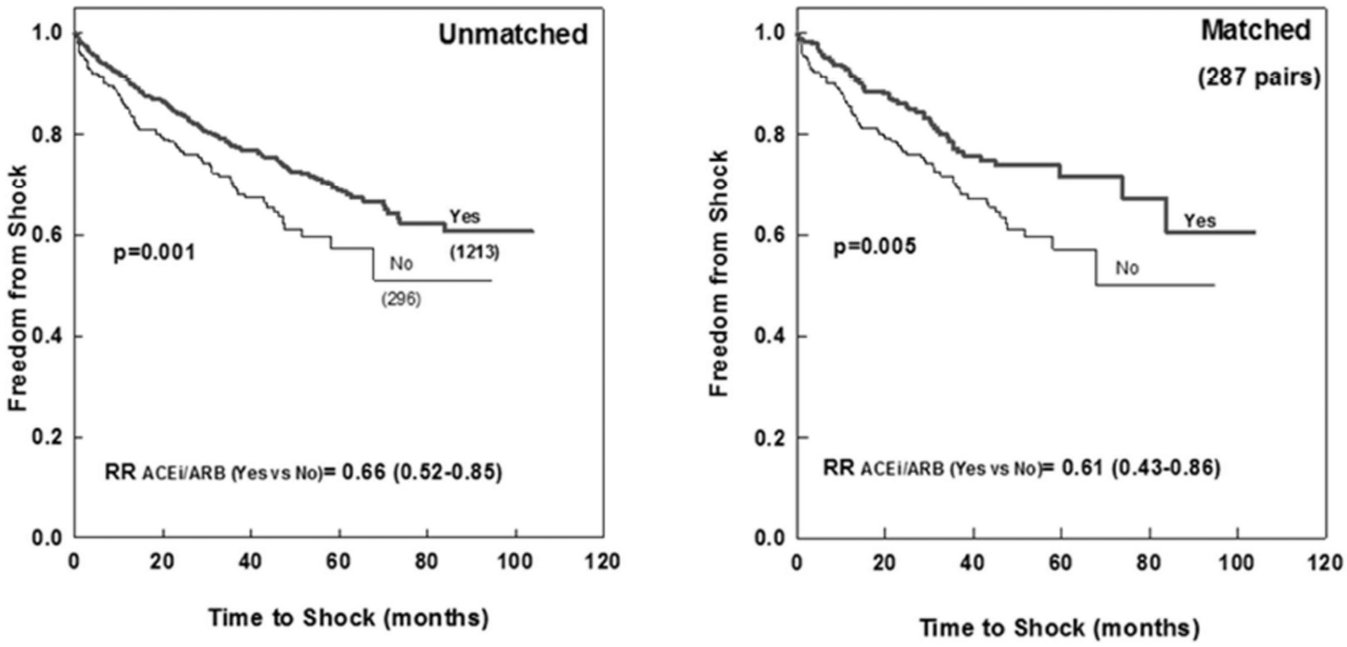

Figure 1.

Freedom from appropriate ICD shock in ACEi/ARB versus No-ACEi/ARB patient subcohorts: All patients (left) and propensity matched sub-cohorts (right).

Numbers in brackets represent the number of patients in each group. p-value represents log rank significance level ACEi (angiotensin converting enzyme inhibitor); ARB (angiotensin receptor blocker); ICD (implantable cardiac defibrillator)

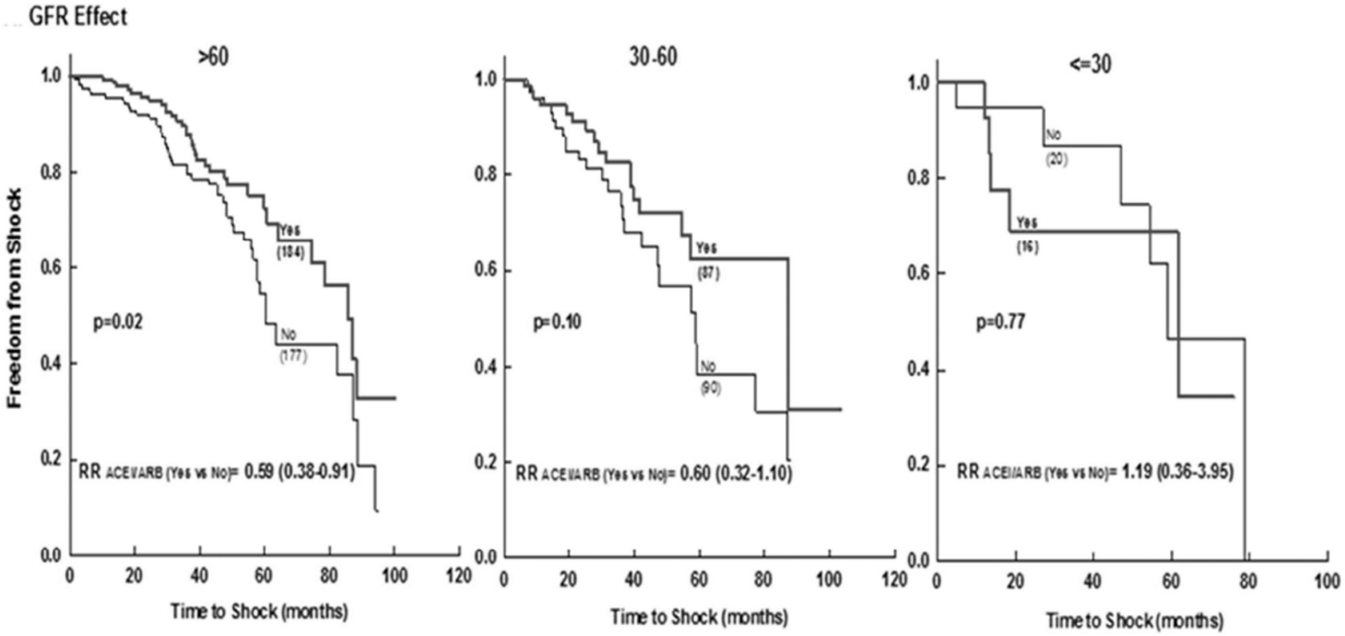

Figure 2.

Freedom from appropriate ICD shock in ACEi/ARB versus No-ACEi/ARB in matched patient subcohorts stratified by glomerular filtration rate.

ACEi (angiotensin converting enzyme inhibitor); ARB (angiotensin receptor blocker); GFR (glomerular filtration rate); ICD (implantable cardiac defibrillator).

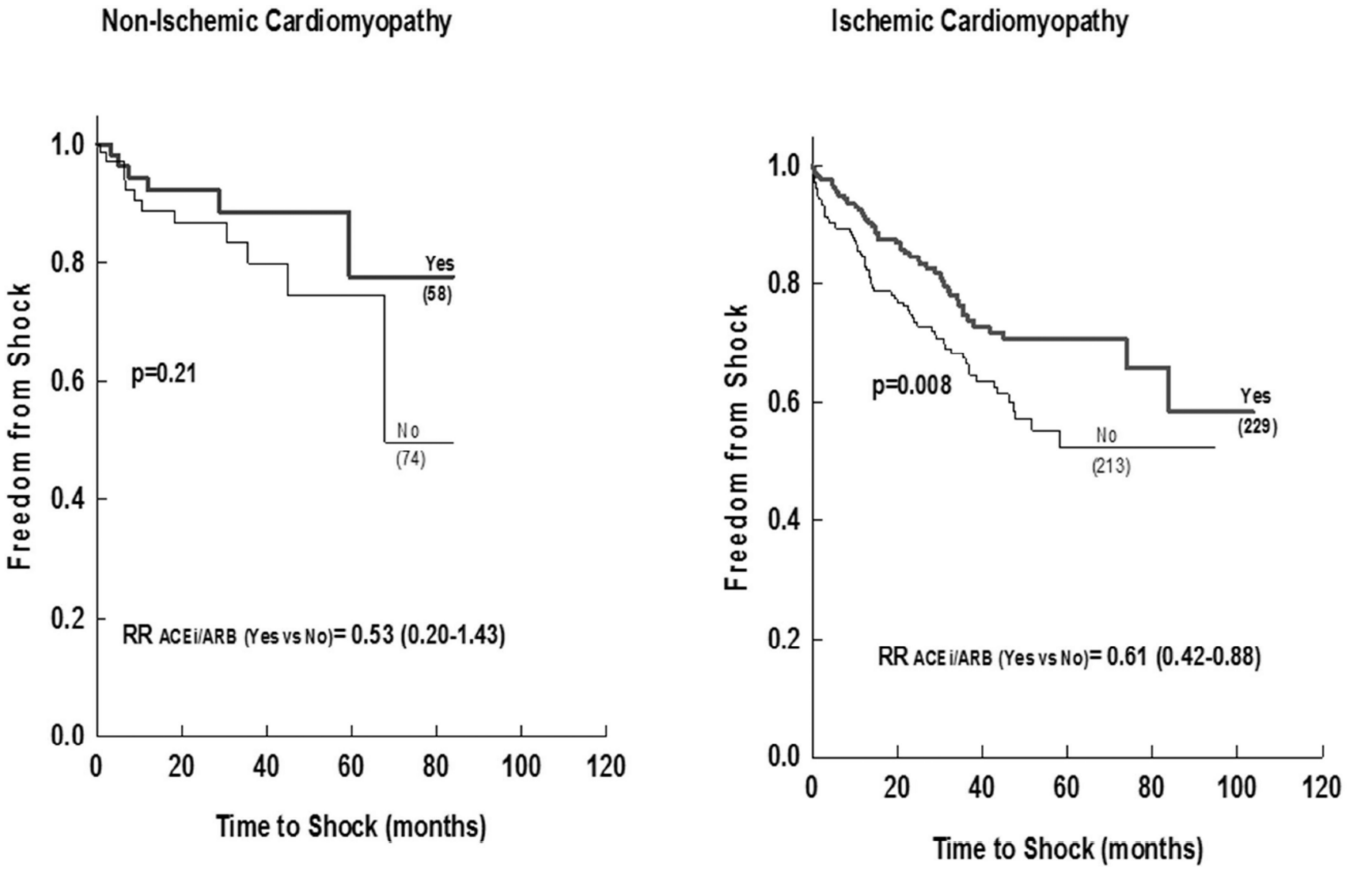

Figure 3.

Freedom from appropriate ICD shock in ACEi/ARB versus No-ACEi/ARB in matched patient subcohorts stratified to Ischemic versus Non ischemic cardiomyopathy.

Numbers in brackets represent the number of patients in each group. p-value represents log rank significance level ACEi (angiotensin converting enzyme inhibitor); ARB (angiotensin receptor blocker); ICD (implantable cardiac defibrillator) GFR (glomerular filtration rate).

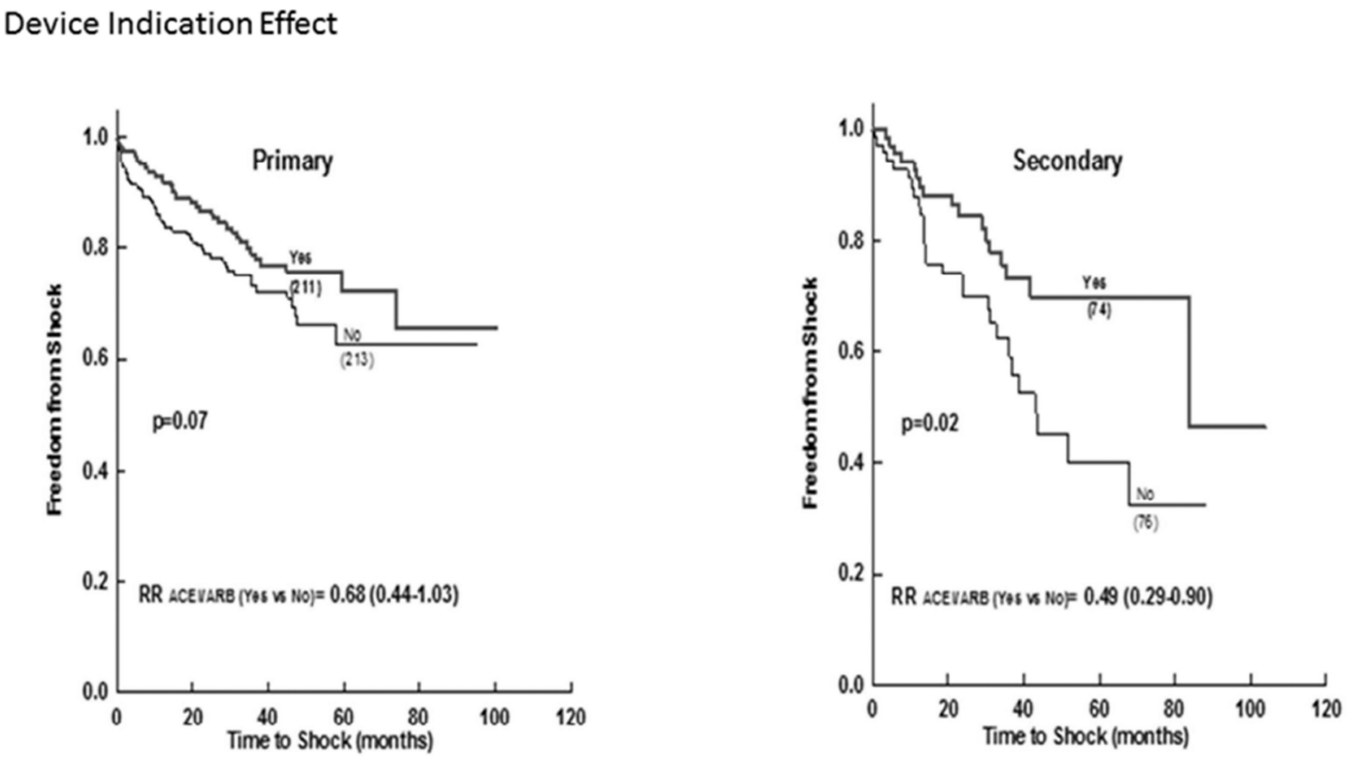

Figure 4.

Freedom from appropriate ICD shock in ACEi/ARB versus No-ACEi/ARB in matched patient subcohorts stratified by indication for device implantation.

ACEi (angiotensin converting enzyme inhibitor); ARB (angiotensin receptor blocker); ICD (implantable cardiac defibrillator).

Table 1

Baseline characteristics stratified by ACEi/ARB

		Un Matched Cohort						Propensity Matched Cohort				
		ACEi/ARB (N=1213)		No ACEi/ARB (N=296)				ACEi/ARB (N=287)		No ACEi/ARB (N=287)		
Variable		**Mean**	**SD**	**Mean**	**SD**	**Diff**	**p-value**	**Mean**	**SD**	**Mean**	**SD**	**Diff**
Age (years)		63	12	64	12	8.9%	0.2	65	12	64	12	8.1%
Systolic Blood Pressure (mm Hg)		120	19	129	18	2.6%	0.7	120	19	120	18	1.8%
Glomerular filtration rate (imputed), (ml/min/1.73m^2)		63	20	58	20	25%	**<.001**	60	18	59	19	3.6%
Glomerular filtration rate(unimputed), (ml/min/1.73m^2)		64	24	57	23	32%	**<.001**	59.0	22	58	23	4.4%
Ejection Fraction (%)		21	6	20	6.0	9.0%	0.2	20	6	20	6	2.3%
QRS interval (ms)		136	36	135	33	3.0%	0.7	135	36	136	34	2.3%
QTC interval (ms)		472	52	471	54	2.7%	0.6	468	49	471	54	6.3%
		N	**%**	**N**	**%**	**Diff**	**p-value**	**N**	**%**	**N**	**%**	**Diff**
Men		981	81%	230	78%	7.8%	0.22	229	80%	224	78%	4.3%
White		1035	85%	239	81%	12%	0.05	235	82%	234	82%	0.9%
Age (years)	< 50	152	13%	31	11%	6.5%	0.36	28	10%	30	11%	2.3%
	50–59	296	24%	71	24%	1.0%		61	21%	69	24%	6.7%
	60–69	407	34%	92	31%	5.3%		97	34%	88	31%	6.7%
	≥ 70	358	30%	102	35%	11%		101	35%	100	35%	0.7%
Body mass index (kg/m^2)	<21	46	4%	12	4%	1.4%	0.92	8	3%	12	4%	7.6%
	21–25	194	16%	50	17%	2.4%		54	19%	49	17%	4.5%
	25–30	512	42%	132	45%	4.8%		127	44%	129	45%	1.4%
	30–35	286	24%	64	22%	4.7%		69	24%	60	21%	7.5%
	35–40	120	10%	25	8%	5.0%		19	7%	25	9%	7.9%
	>40	55	5%	13	4%	0.7%		10	4%	12	4%	3.6%
Glomerular filtration rate (ml/min/1.73m^2)	>60	177	60%	845	70%	21%	**<.001**	184	64%	177	62%	5.0%
	30–60	93	31%	327	27%	9.6%		87	30%	90	31%	2.3%
	<30	26	9%	41	3%	23%		16	6%	20	7%	6%
New York Heart Association class	I	151	12%	52	18%	14%	**0.045**	42	15%	52	18%	9.4%
	II	728	60%	156	53%	15%		160	56%	152	53%	5.6%

		Un Matched Cohort						Propensity Matched Cohort				
		ACEi/ARB (N=1213)		No ACEi/ARB (N=296)				ACEi/ARB (N=287)		No ACEi/ARB (N=287)		
	III	324	27%	87	29%	6.0%		85	30%	82	29%	2.3%
	IV	10	.8%	1	.3%	6.4%		0	0%	1	0.3%	8.4%
Ischemic etiology		854	70%	221	75%	9.6%	0.15	229	80%	213	74%	13.3%
Device Indications	Secondary	292	24%	77	26%	4.5%	0.49	74	26%	76	27%	1.6%
Defibrillator with biventricular pacing		523	43%	136	46%	5.7%	0.38	123	43%	131	46%	5.6%
Prior myocardial infarction		649	54%	169	57%	7.2%	0.27	173	60%	162	56%	7.8%
Diabetes mellitus		404	33%	116	39%	12%	0.06	119	42%	110	38%	6.4%
Hypertension		778	64%	181	61%	6.2%	0.34	179	62%	176	61%	2.2%
Hyperlipidemia		784	65%	188	64%	2.3%	0.7	184	64%	182	63%	1.5%
Smoker		632	52%	154	52%	0.2%	0.99	149	52%	148	52%	0.70%
Medications	Beta Blockers	1043	86%	243	82%	11%	0.09	233	81%	238	83%	4.5%
	Diuretics	881	73%	207	70%	6.0%	0.35	189	66%	203	71%	10.5%
	Aldactone/Eplerenone	336	28%	69	23%	10%	0.13	69	24%	68	24%	0.82%
	Digoxin	572	47%	107	36%	23%	**0.001**	108	38%	105	37%	2.2%
	Anti-Arrhythmics	249	21%	63	21%	1.9%	0.77	62	22%	62	22%	0.0%
	Amiodarone	194	16%	55	19%	6.9%	0.28	51	18%	54	19%	2.7%

Diabetes mellitus was defined as fasting blood glucose >126 mg/dl or HbA1c ≥6.5 or taking hypoglycemic agents or insulin. Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or taking anti-hypertensive medication. Hyperlipidemia was defined as elevated total cholesterol or low-density lipoprotein levels above the goals set by the ATPIII or taking cholesterol lowering agents.

Table 2

Baseline characteristics stratified by presence or absence of appropriate shock

Variable		SHOCK (N=334)		NO SHOCK (N=1175)		
		Mean	**SD**	**Mean**	**SD**	**p-value**
Age (years)		61	12	63	12	0.006
Systolic Blood Pressure (mm Hg)		117	18	120	19	0.004
Glomerular filtration rate (ml/min/1.73m^2)		61	20	62	20	0.290
Ejection Fraction (%)		20	6	21	6	<.001
QRS interval (ms)		140	35	135	35	0.015
QTC interval (ms)		475	52	471	53	0.330
		N	**%**	**N**	**%**	**p-value**
Men		285	85%	926	79%	0.01
White		272	81%	1002	85%	0.10
Age (years)	< 50	50	15%	133	11%	0.16
	50–59	88	26%	279	24%	
	60–69	101	30%	398	34%	
	≥ 70	95	28%	365	31%	
Body mass index (kg/m^2)	<21	11	3.3%	47	4.0%	0.16
	21–25	43	13%	201	17%	
	25–30	155	46%	489	42%	
	30–35	71	21%	279	24%	
	35–40	40	12%	105	8.9%	
	>40	14	4.2%	54	4.6%	
Glomerular filtration rate (ml/min/1.73m^2)	>60	213	64%	809	69%	0.08
	30–60	100	30%	320	27%	
	<30	21	6.3%	46	3.9%	
New York Heart Association class	I	45	14%	158	13%	0.76
	II	189	57%	695	59%	
	III	97	29%	314	27%	
	IV	3	0.9%	8	0.7%	
Ischemic etiology		252	75%	823	70%	0.05

Variable		SHOCK (N=334)		NO SHOCK (N=1175)		
Device Indications	Secondary	102	31%	267	23%	0.00
Defibrillator with biventricular pacing		138	41%	521	44%	0.33
Prior myocardial infarction		190	57%	628	53%	0.27
Diabetes mellitus		112	34%	408	35%	0.69
Hypertension		196	59%	763	65%	0.04
Hyperlipidemia		221	66%	751	64%	0.45
Smoker		178	53%	608	52%	0.62
Medications	ACEi/ARB	252	75%	961	82%	0.01
	Beta Blockers	281	84%	1005	86%	0.53
	Diuretics	253	76%	835	71%	0.09
	Aldactone/Eplerenone	99	30%	306	26%	0.19
	Digoxin	170	51%	509	43%	0.01
	Antiarrythmics	96	29%	216	18%	<.001
	Amiodarone	77	23%	172	15%	<.001

Definitions as in table 1.

Table 3

Independent Predictors of Shock on Multivariate Cox Proportional Hazard Model

	Unmatched (N=1509)		Propensity Matched (N=574)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
ACEi/ARB *GFR		<.001		0.046
ACEi/ARB (+), GFR (>60 ml/min/1.73m^2)	1.0 (Ref)	---	1.0 (Ref)	---
ACEi/ARB (+), GFR (30–60 ml/min/1.73m^2)	1.28 (0.96–1.69)	0.09	1.17 (0.65–2.11)	0.61
ACEi/ARB (+), GFR (<30 ml/min/1.73m^2)	2.35 (1.32–4.19)	0.004	1.81 (0.69–4.78)	0.23
ACEi/ARB (−), GFR (>60 ml/min/1.73m^2)	1.45 (1.05–2.01)	0.02	1.68 (1.08–2.62)	0.02
ACEi/ARB (−), GFR (30–60 ml/min/1.73m^2)	2.05 (1.32–3.16)	0.001	2.15 (1.26–3.66)	0.005
ACEi/ARB (−), GFR (<30 ml/min/1.73m^2)	2.41 (1.18–4.95)	0.02	2.34 (0.96–5.66)	0.06
Age (years)	0.98 (0.97–0.99)	<.001	0.98 (0.97–0.99)	0.04
Systolic Blood Pressure (mm Hg)	0.99 (0.99–1.00)	0.03	---	---
Ejection Fraction (%)	0.98 (0.96–0.99)	0.04	0.97 (0.94–0.99)	0.03
QRS (ms)	1.004(1.001–1.007)	0.02	1.005 (1.00–1.01)	0.05
Women	0.70 (0.51–0.97)	0.03	---	---
Race (African American)	1.65 (1.23–2.23)	0.001	---	---
Ischemic etiology	1.39 (1.05–1.84)	0.02	2.16 (1.29–3.62)	0.003
Digoxin	1.24 (0.97–1.55)	0.054	---	---
Anti-arrhythmics	1.60 (1.25–2.04)	<.001	1.44 (0.98–2.10)	0.06