Impact of Guideline-Based Medical Therapy on Malignant Arrhythmias and Mortality among Heart Failure Patients Implanted with Cardioverter Defibrillator (ICD) or Cardiac Resynchronization-Defibrillator device (CRTD)

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Abstract

Aim: To evaluate prevalence of heart failure (HF) medical treatment and its impact on ventricular arrhythmia (VA) and survival among patients implanted with primary prevention ICD/CRTD. Methods and results: The association of treatment and dose (% guideline recommended target) of beta-blockers (BB), Angiotensin-antagonists (AngA), Mineralocorticoid-antagonsits (MRA), and Anti-Arrhythmic Drugs (AAD) after ICD/CRTD implant with VA episodes and mortality was analyzed. We included 186 patients, mean?SD age 66.4?12 years, 15.1% female, 79(42.5%) implanted with an ICD and 107(57.5%) with CRTD. During 3.8 [2.1;6.7] (median[IQR]) years; 52(28%) had VA and 77(41.4%) died. Treatment (medication, % of patients) included: BB (83%), AngA (87%), MRA (59%), and AAD (43.5%). Median doses were 25[12.5;50]% of target for BB or AngA and 25[0;50]% of target for MRA. Treatment with >25% target dose of BB was associated with reduced incident VA. In a multivariable model including age, gender, diabetes, heart rate, and medication doses, increased BB dose was significantly and independently associated with reduced VA (HR 0.443 95%CI 0.222-0.885; p=0.021). On multivariable model for overall mortality including age, gender, renal disease, VA, and medical treatment; VA was associated with increased mortality (HR 2.672; 95% CI 1.429-4.999; p=0.002) and AngA treatment was significantly and independently associated with reduced mortality (HR 0.515; 95% CI 0.285-0.929; p=0.028). Conclusions: In this cohort of real-life HF patients discharged after ICD/CRTD implant, most of the patients were prescribed with guideline-based HF medications albeit with low doses. Higher BB dose was associated with reduced VA, while treatment with AngA was associated with improved survival.

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Short title: Importance of HF treatment among defibrillator implantees

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Conclusions : In this cohort of real-life HF patients discharged after ICD/CRTD implant, most of the patients were prescribed with guideline-based HF medications albeit with low doses. Higher BB dose was associated with reduced VA, while treatment with AngA was associated with improved survival.

Key words: Heart failure, medical treatment, defibrillator, arrhythmia

What is already known?

1. Majority of heart failure (HF) guideline recommended medications were proved to reduce HF hospitalization and overall mortality.

2. ICD and CRTD primary prevention implant in symptomatic HF patients with low EF with narrow and wide LBBB, respectively, were sown to reduced overall mortality.

3. The impact of HF medication regarding ventricular arrhythmia is less robust.

What does this paper add?

1. Most heart failure (HF) patients implanted with a primary prevention ICD/CRTD device were prescribed with guideline-based HF medications albeit with low doses (with regard to HF guidelines-recommended target dose).

2. Patients who were followed via a specialized HF clinic had better HF treatment.

3. A significant correlation found between increased BB dosage and reduced ventricular arrhythmias occurrence.

4. Treatment by Angiotensin Antagonists was associated with reduced overall mortality.

Introduction

Adherence to Heart failure (HF) guideline recommended medical treatment was shown to reduce HF symptoms, hospitalizations, and all-cause mortality in previous publications (1-10). Although the impact of such treatment on reduced ventricular arrhythmia (VA) and sudden cardiac death (SCD) was suggested (1,8,11,12,13), this was not evaluated as a primary outcome in randomized clinical trials but rather as a secondary outcome (1,8) or in the context of a meta-analysis (11-14). Circumstantial evidence suggests that combination HF therapy reduces SCD rate and might mitigate the added survival benefit of an implantable cardiac defibrillator (ICD) device among HF patients in general and specifically among non-ischemic dilated cardiomyopathy (DCM) patients, in whom the evidence for survival benefit with an ICD is weaker (15,16). A meta-analysis of pivotal HF trials has shown a continuous decline of SCD incidence as the trails became more recent. This observation was attributed to the increased utilization of HF guideline-based medications in the recent trials compared with the older ones (15). Moreover, among DCM patients in the DANISH trial (16) there was no significant mortality difference between patients treated with optimal medical management including cardiac resynchronization therapy (CRT) as appropriate and those treated similarly with additional ICD. Again, suggesting that current guideline-based medical therapy may obviate the need of an ICD in selected patients. This finding was reinforced in a recent meta-analysis of randomized trials evaluating the survival benefit of ICD in DCM patients, revealing loss of the survival benefit in trials where >50% of patients were taking a combination of beta adrenergic receptor antagonist (BB), Angiotensin antagonist (ACEi/ARB), and mineralocorticoid receptor antagonist (MRA) (14). In contrast with the above mentioned HF trials, large registries of HF patients have shown relatively low percent of patients treated with optimal HF medical therapy (17-20).

The aim of the current study was to evaluate the prevalence of HF medical therapy and its impact on VA incidence and overall mortality among contemporary primary prevention ICD/CRTD recipients.

Methods

Study patients

HF Patients hospitalized at Shaare Zedek Medical Center between the years 2007-2017 for de novo ICD or CRTD implant and who were followed at our hospital's device clinic were included.

Inclusion criteria were therefore:

Primary prevention implant of an ICD or CRTD

At least 4 device clinic visits during the study follow up period.

Exclusion criteria were:

- Device upgrade during the study follow-up period

- Implant at another center (incomplete device interrogation data)

- Previous sustained VA or cardiopulmonary resuscitation.

Eligible patient's data were reviewed by a senior cardiologist that confirmed their indication for primary prevention ICD/CRTD according to current guidelines (21-23) and the absence of exclusion criteria. Medical

treatment was determined based on medical prescriptions in the discharge letter of the index hospitalization (hospitalization in which ICD/CRTD was implanted). Guideline-recommended disease modifying HF medications were grouped according to mechanism of action as beta adrenergic blockers (BB), angiotensin antagonists (AngA) including angiotensin receptor blockers (ARB) or angiotensin conversion enzyme inhibitors (ACE-I), and mineralocorticoid receptor antagonist (MRA). All anti-arrhythmic drugs (AAD) used were documented as well. The prevalence of each medication group among study patients was noted. The proportion of each HF medication dose to the guideline recommended target dose (23) was calculated and reported as % target dose.

As previous studies suggested beneficial survival effects for taking >50% target dose of AA and BB (20,24), we initially planned to examine and compare medication dose effect by 50% target dose cutoff. However, since the median dose for all 3 medication groups in our study was 25% of target dose with relatively few patients taking >50%, we used the median dose cutoff to examine the effect of medications' dose on study outcomes.

Outcomes

Outcomes included VA and all-cause mortality. Follow up for outcomes was initiated from the index hospitalization, when ICD/CRTD was implanted, until mortality or last documented visit to HF or device clinic. VA was defined as any VA episode for which an appropriate ATP or shock therapy was delivered by the ICR/CRTD device, as detected during device clinic follow-up. Device clinics were routinely scheduled 1,3 and every 6 months after device implant. During clinic visit, all VA episodes were retrieved from the device and any treatment (ATP, shock or both) was documented. When multiple VAs occurred, the first one was considered for study outcome. Devices were programmed in a 'primary prevention' mode (similar in all device companies), in accordance with the updated expert consensus on optimal ICD programming (25), consisting of the following detection zones and therapies: VF therapy zone > 200-220 bpm for 24-30 beats, treated via ATP during charge and thereafter device shocks; VT_2 therapy zone > 185 bpm for 30 beats or 12 sec duration (BSC devices), treated via [?]1 ATP burst and thereafter device shocks; and a VT_1 monitor zone >160 bpm used for monitoring only. Mortality was determined from the Israeli Ministry of the Interior records. The study was approved by the local institutional review board.

Statistical analysis

Categorical data are represented as proportions, continuous data as mean +- SD for normally distributed variables or median and interquartile range for non-normal distribution. Comparisons were made using Chi-Square Test, Fisher's exact test, unpaired student T-test and Mann-Whitney test. Multivariable COX proportional hazard models were used to identify independent characteristics and medical treatment associated with VA or mortality. To assess the impact of VA on overall mortality a Cox model with time to first VA as a time dependent covariate was used. Unadjusted and adjusted Hazard ratios (HRs) with 95% confidence intervals (CIs) were displayed. All tests were two sided, p-values < 0.05 were considered statistically significant. Analyses were carried out using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY.

Results

There were 186 patients implanted with an ICD/CRTD between the years 2007-2017 that matched the study's inclusion criteria (Figure 1). Their mean age was 66.4+-12 years, 15.1% were female. ICD was implanted in 79 (42.5%) and a CRTD in 107 (57.5%). Median [IQR] follow-up time was 3.8 [2.1-6.7] years. Patient characteristics are shown in table 1. There were 52 (28%) patients with VA, including VT in 31/52 patients (59.5%), VF in 6/52 patients (11.5%) or both in 15/52 patients (29%). These VA cases were treated successfully by anti-tachycardia pacing (ATP) in 22 (42.4%) patients and by device shock in 30 patients (57.6%). There were 77 (41.4%) deaths during the study F/U period. The prevalence of HF medication treatment at index hospitalization discharge was: 155/186 (83.3%) BB, 162/186 (87.1%) AngA, and 110/186 (59.1%) MRA. AAD were prescribed in 81/186 (43.5%) patients. Doses (% target) of HF medication were: 32+-25% for BB, 38.2+-30% for AA and 31+-30% for MRA. The median dose (% target dose) for all 3 guideline-based medication groups included in our study was 25% (Table 2). Few patients were prescribed

with >50% of target dose: 18/155 (11.6%), 34/162 (21%), and 16/110 (14.5%) of patients taking >50% target dose of BB, AngA, and MRA, respectively (Table 2).

Only 18/186 (9.7%) of study patients were followed regularly in the hospital's HF clinic by HF specialist (most patients were followed regularly by their general cardiologists and came to our hospital only for device clinic interrogations). There were more patients treated by BB among the group followed in HF clinic (100% vs 81.5%, p=0.046) and their dose (% target dose) was higher (61.1% vs. 33.9%, p=0.023). There was a non-significant trend for higher prevalence of AngA (88.9% vs. 86.9%, p=0.81) and MRA (72.2% vs. 57.7%, p=0.23) among those followed at HF clinic as well.

Association of HF medical treatment with VA

Comparing patients with documented VA to those without VA, revealed similar baseline characteristics, except for lower prevalence of Diabetes Mellitus (DM) and longer follow-up among the VA group (Table 1). Crude medication prescription was not associated with VA, nor was the number of guideline-based medications (2.3+-0.83 for VA vs. 2.25+-0.7 without VA; p =0.8). Patients taking all 3 guideline-recommended medication groups did not have less VA (p 0.33). The patients with VA were treated with significantly lower doses of BB compared to those without VA (23.9+-19% versus 35.5+-27% target dose; p=0.012). There was no significant difference in AA or MRA doses between the VA and no VA groups (Table 1).

Incident VA was significantly less common among patients treated by >25% target dose of BB as compared to those treated with [?] 25% target dose (17.6% vs. 33.9%, p 0.017). This was not observed in patients taking >25% AngA (30% vs. 26% p 0.55) or MRA (29.5% vs. 26.5% p=0.64) compared to those treated by [?] 25% target dose of these medications. Kapkan-Myer (KM) analysis for survival without VA according to each medication group dose, supported reduced VA among patients receiving > median dose of BB (Figure 2).

Univariate parameters found to be significantly associated with incident VA were: heart rate at admission (HR 1.02; 95% CI 1.00-1.04; p=0.02), DM (HR 0.42; 95% CI 0.23-0.78; p=0.006), and BB >25% target dose (HR 0.51; 95% CI 0.27-0.98; p=0.04). In Cox multivariable model for VA including age, gender, DM, medication dosage (>25% target dose), and heart rate, both BB dose > median dose (HR 0.443, 95% CI 0.222-1.022; p=0.021) and DM (HR 0.454, 96% CI 0.237-0.868; p=0.017) were significantly and independently associated with lower incidence of VA; while increased heart rate was significantly associated with VA (HR 1.03, 95% CI 1.009-1.049; p=0.004) (Table 3).

HF medication prescription and overall survival

Potential predictors of mortality are presented in Table 4. Older age at device implant, renal dysfunction, CRTD implant (rather than ICD), and VA episodes during F/U were associated with increased overall mortality. Analysis of HF medications showed that combined treatment with all 3 HF medication groups (p=0.0047) and treatment with AngA per se (p 0.028), regardless of dose, were significantly associated with reduced mortality (Table 4).

In a univariate analysis the following parameters were significantly associated with overall mortality: age (HR 1.06; 95% CI1.04-1.09; p=0.0001), renal dysfunction (HR 1.63; 95% CI1.03-2.56; p=0.037), CRTD (versus ICD) (HR 1.67; 95% CI1.03-2.71; p=0.036), VA during F/U (HR 2.76; 95% CI 1.474-4.967, p=0.001) and AngA treatment (HR 0.55; 95% CI 0.31-0.97; p=0.039).

In Cox multivariable survival analysis including patients' age, gender, renal function, HF medication treatment, and VA occurrence during F/U, AngA treatment (but not BB or MRA) was significantly associated with reduced mortality (HR 0.515; 95% CI 0.285-0.929; p=0.028); while age (HR 1.06; 95% CI 1.038-1.093; p=0.0001); renal disease (HR 1.728; 95% CI 1.070-2.792; p=0.025); and VA during F/U (HR 2.672; 95% CI 1.429-4.999; p=0.002) were significantly associated with increased mortality (Table 5).

Kaplan-Myer overall survival analysis according to HF medication groups showed reduced mortality among patients with AngA (p=0.036) without significant impact of BB or MRA (Figure 3). Interestingly, Kaplan-

Myer overall survival curves for the combination of all 3 HF medication groups diverged for improvement with combined treatment after 4 years (curve not shown). Kaplan-Myer overall survival curves by incident VA (as a competing event) revealed increased mortality in patients with VA (Figure 4).

Discussion

This study, including 186 HF patients implanted with a primary prevention ICD or CRTD and meticulously followed in the device clinic, evaluated the impact of guideline-based HF medications on incident VA and total mortality. During the median F/U period of 3.8 years, 28% of the patients had VA and 41.4% died. On the whole, although most of the patients were prescribed with the appropriate HF medications ($> 80\%$ for BB and AngA and 60% for MRA), the doses were low. The median dose of HF medications in the current study was 25% of target dose for all 3 medication groups with less than 20% of patients treated by >50% target dose. We found that treatment with lower doses of BBs and increased heart rates were both significantly and independently associated with increased VA, while DM was associated with reduced VA incidence. We also found that treatment with AngA was significantly associated with reduced overall mortality, while VA and renal dysfunction were associated with increased mortality.

The incidence of VA in the current study is comparable to previously published studies. In the SCD-HeFT primary prevention trial which had a similar F/U period, the incidence of appropriate ICD shocks was 21.5% (26). The estimated annual incidence of VA in our study of 7.4% is similar to the 7.2% annual appropriate shock incidence in the DEFINITE primary prevention trial (27). Notably, the patients' devices in the current study were routinely programmed via prolonged VA detection periods to enable spontaneous termination of short VAs, as well as device intervention for relatively fast VAs. Thus, only long and fast VAs were included in the current study. Importantly, these clinically relevant VAs do not equal sudden cardiac death, as they might still end spontaneously (28-30). Nevertheless, these VAs do have a significant impact on overall mortality, as was shown in the current study and as supported by several prior studies establishing the benefit of ICD implant (26,27,31-34).

In the current study the dosage of BB, rather than their mere use, was associated with VA reduction. The importance of aiming for target doses was previously studied, revealing increased deaths and/or HF hospitalizations among HF patient treated by $< 50\%$ target dose of BB and ACE-I (7,20,24). The importance of HF medication dosage was further emphasized in the DANISH trial where optimal medical therapy, with medication prevalence of >90% for BB and AA and 60% for MRA (similar to current study) and doses that were increased to target doses whenever possible, were suggested to obviate the survival benefit of an ICD (16). Lastly, a recent meta-analysis including six pivotal randomized trials of DCM patients, showed a significant survival benefit of ICD plus medical therapy compared with medical therapy alone, but this survival benefit was lost in trials where >50% of patients were treated via combination of BB, AngA, and MRA with doses reaching guideline target doses (14). On the whole, our study suggests that HF medication dosage in general and BB dose specifically, is important for reducing VA in advanced HF patients implanted with an ICD or CRTD.

Potential mechanisms for antiarrhythmic effects of BB include their anti-sympathetic effect resulting in reduced heart rates and increased heart rate variability, direct anti-arrhythmic effect, reducing intra-cellular Ca within cardiac cells, improving cardiac function, reducing cardiac ischemia and more (35,36). In the current study, reduced BB doses were associated with increased VA even when adjusting for heart rate. Therefore, BBs may have an anti-arrhythmic effect beyond decreasing heart rate per se. This result is in line with previous trials (37-39), which show that although increased heart rates are associated with worst outcomes in HF patients, increasing BB dose regardless of baseline heart rates is associated with an improved combined outcome of all-cause mortality and HF hospitalizations. Accordingly, we as others (37-39), suggest that BB dose up-titration regardless of baseline heart rate should be considered for VA prevention (as long as symptomatic or excessive bradycardia is absent).

Low dosing of all HF recommended medications was one of main findings in the current study. Low dosing was noticed in multiple HF studies and registries (17-20,24), acknowledging this is a universal problem.

For example, in the CHAMP-HF registry including 3500 HF patients with reduced EF from 150 medical centers, less than 25% of patients received target dose of any HF medication and only 1% received target dose of all 3 HF family medications (17,18). Similarly, only a minority of patients in the Asian (19) and pan-European (24) registries received target doses of any HF medication. Low dose HF medications could result from inadequate medical surveillance, non-referral to specialized HF clinic, or otherwise impacted by various 'obstacles' such as low blood pressure or heart rate, co morbidities, and medication-related side effects preventing one from achieving target doses. In the current study, patients with and without VA had similar co morbidities, with HTN in most patients and heart rates between 70-80 bpm in both groups. Hence, we suggest that the lower BB dosage among patients with VA is not related to sicker patients who cannot tolerate increased BB doses but rather suboptimal medical surveillance. This corroborates with the limited number of study patients who were followed in the HF clinic (enjoying better adherence to treatment). Indeed, in reality many ICD/CRTD candidates are referred to an EP clinic by their general cardiologists or GPs for device implantation without HF consultation and with inadequate HF medical treatment. Thus, we suggest that all HF patients and especially those referred to device implant undergo HF specialist consultation, aiming to achieve HF medication target doses. Importantly, this approach is strongly supported by both EP and HF guidelines advocating ICD or CRTD implant only after confirmation of optimal HF medical treatment (21-23).

Strengths and Limitations

Our study has several limitations including: a) its retrospective nature; b) single center data; c) the overall low doses of guideline-based medications, resulting in possible underestimation of medication effect; d) discharge prescriptions may not equal true medical treatment over time, although most patients remain treated with their discharge recommendations; e) most study patients were included prior to 2016 and thus were not treated with angiotensin receptor/neprilysin inhibitors (ARNI). Thus, our study did not evaluate impact of ARNI, which is a pivot HF medication in recent years; f) data on cause of death is missing. The study also has several strengths including the meticulous retrieval of VA events and the in-depth manual evaluation of discharge medication dose analyzed as the proportion of guideline recommendations.

Conclusion:

In this single center retrospective cohort of CHF patients implanted with an ICD/CRTD for primary prevention, we found a relatively high prevalence of HF guideline-recommended medication treatment albeit with low doses. Reduced BB doses were associated with an increased VAs which in turn are associated with increased mortality, while treatment with AngA was associated with reduced overall mortality. Specialized HF consultation is therefore advocated for these patients referred for primary prevention ICD/CRTD to improve their medical treatment and outcomes.

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Table 1 - Patient characteristics and comparison of patients with and without VA

Parameter	Total (n=186)	VA (n=52)	No VA (n=134)	p
Age	66.4±12	66.8±11.8	66.7±11.7	0.7
Gender (Male)	158 (84.9%)	48 (92.3%)	110 (82.1%)	0.08
Heart Rate (admission)	72.5±14	75.7±16	71.4±12	0.068
ICD	79 (42.5%)	26 (50%)	53 (39.6%)	0.22
CRTD	107 (57.5%)	26 (50%)	81 (60.4%)	0.2
Ischemic CM	115 (61.8%)	29 (55.7%)	86 (64.1%)	0.25
HTN	130 (69.8%)	35 (67.3%)	95 (70.8%)	0.7
DM	79 (42.4%)	14 (26.9%)	65 (48.5%)	0.008
Renal dysfunction	66 (35.4%)	17 (32.7%)	49 (36.5%)	0.7
Number of guideline-based medications	2.3±0.75	2.3±0.83	2.25±0.7	0.8
BB treatment	155 (83.3%)	40 (79.6%)	115 (85.8%)	0.14
BB dose (% target)	32±25%	23.9±19%	35.5±27%	0.012
BB > 25% target dose	68 (36.5%)	12 (23%)	56 (41.8%)	0.084
AngA treatment	162 (87.1%)	46 (88.5%)	116 (86.6%)	0.73
AngA dose (% target)	38.2±30%	41.2±32%	37±30%	0.38
AngA > 25% target dose	90 (48.3%)	27 (51.9%)	63 (47%)	0.943
MRA treatment	110 (59.1%)	31 (59.6%)	79 (59%)	0.93

Parameter	Total (n=186)	VA (n=52)	No VA (n=134)	p
MRA dose (% target)	31±30%	32.2±30.8%	30.4±30%	0.74
MRA > 25% target dose	88 (47.3%)	26 (50%)	62 (46.3%)	0.932
AAD treatment	81 (43.5%)	22 (42.3%)	59 (44%)	0.83
BB+AngA+MRA treatment	86 (46.2%)	21 (40.4%)	65 (48.5%)	0.33
Follow up period (median[IQR], days)	1399 [752,2432]	1819 [930,3140]	1326 [679,2113]	0.005

Table 2- HF medication groups prevalence and doses

Medication	Prevalence N (%)	Median [IQR] Dose (% target)	Dose (% target) Average ± SD	Patients receiving > 50% target dose
BB	155 (83.3%)	25 [12.5;50]	32 ± 25%	18/155 (11.6%)
AngA	162 (87.1%)	25 [12.5;50]	38.2 ± 30%	34/162 (21%)
MRA	110 (59.1%)	25 [0;50]	31 ± 30%	16/110 (14.5%)

Table 3- Cox proportional- hazards multivariate model for ventricular arrhythmia

Parameter	HR	95% CI	P
Age upon admission (years)	.999	0.977-1.022	.944
Gender (Male)	.388	0.138-1.092	.073
Diabetes Mellitus	.454	0.237-0.868	.017
Heart Rate admission	1.029	1.009-1.049	.004
BB > 25% target dose	.443	0.222-0.885	.021
AngA > 25% target dose	1.010	0.559-1.827	.973
MRA > 25% target dose	1.407	0.783-2.528	.254

Table 4: Characteristics of patients who died or survived follow-up

Parameter	Died (n=77)	Survived (n=109)	p
Age (years)	71.1±11	63.1±11.6	0.0001
Male	70 (90.9%)	88 (80.7%)	0.063
ICD	25 (32.4%)	54 (49.5%)	0.024
CRTD	52 (67.5%)	55 (50.4%)	0.024
Ischemic Cardiomyopathy	54 (70.1%)	61 (55.9%)	0.065
Hypertension	56 (72.7%)	74 (67.8%)	0.5
Diabetes mellitus	28 (36.3%)	51 (46.7%)	0.17
Renal dysfunction	34 (44.2%)	32 (29.3%)	0.043
VA during F/U	31 (40.2%)	21 (19.2%)	0.0028

Parameter	Died (n=77)	Survived (n=109)	p
Number of guideline-based medications	2.13±0.75	2.41±0.74	0.007
BB treatment	61 (79.2%)	94 (86.2%)	0.23
BB dose (% target)	29.3%±24%	34.3±27%	0.243
BB > 25% target dose	26 (33.8%)	42 (38.5%)	0.506
AngA treatment	62 (80%)	100 (91.7%)	0.028
AngA dose (% target)	37.6±31%	39.3±28%	0.389
AngA > 25% target dose	37 (48.1%)	53 (48.6%)	0.94
MRA treatment	41 (53.2%)	69 (63.4%)	0.17
MRA dose (% target)	28.2±30%	32.8±29%	0.169
MRA > 25% target dose	30 (39%)	58 (53.2%)	0.055
AAD rate	31 (40.2%)	50 (45.8%)	0.45
BB+AngA+MRA treatment	26 (33.7%)	60 (55%)	0.0047
Follow up period (median[IQR], days)	1398 [567,2361]	1400 [805,2434]	0.27

Table 5- Cox proportional-hazards multivariate model for overall mortality

Parameter	HR	95% CI	P
Age upon admission (years)	1.065	1.038-1.093	.0001
Gender (Male)	.666	0.298-1.488	.321
Renal disease	1.728	1.070-2.792	.025
VA (any episode)	2.672	1.429-4.999	.002
BB treatment	1.269	0.711-2.265	.421
AngA treatment	.515	0.285-0.929	.028
MRA treatment	1.479	0.915-2.392	.110

Figure Legends

Figure 1: Study subjects depicting inclusion and exclusion criteria.

Figure 2: Survival without ventricular arrhythmia (VA) KM curves according to heart failure medications dose (> or [?] median dose), showing significantly less VA among patients taking > median dose of beta adrenergic blockers, with no significant impact of angiotensin antagonists or mineralocorticoid receptor blockers medication dosages on VA occurrence. P<0.05 is considered significant.

Figure 3: Overall survival KM curves according to heart failure medication treatment (regardless of dose) revealing reduced mortality in patients treated with angiotensin antagonists. P<0.05 is considered significant.

Figure 4: Survival KM curves according to presence or absence of VA, as a time dependent covariate. Occurrence of VA had a significant impact, increasing overall mortality. P<0.05 is considered significant.

Figure 1- Study patients

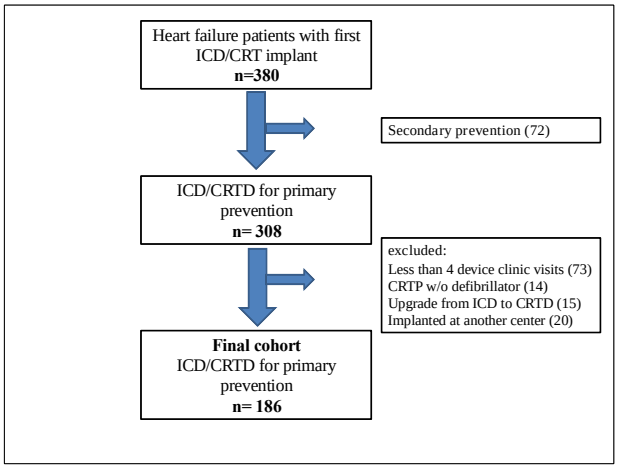

Figure 2: Survival without ventricular arrhythmia KM curves according to HF medication doses

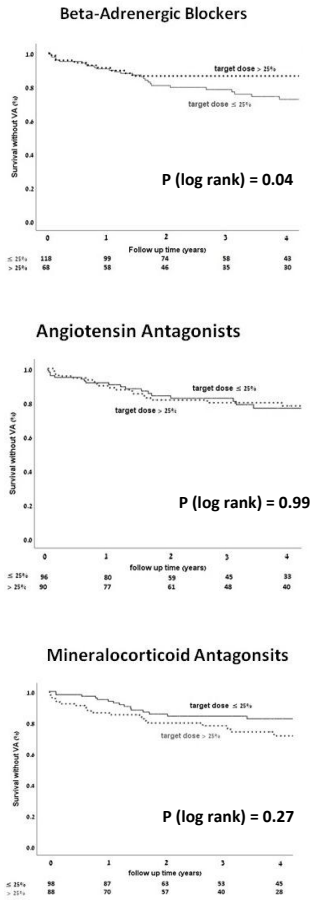

Figure 3: Overall survival KM curves according to HF medication

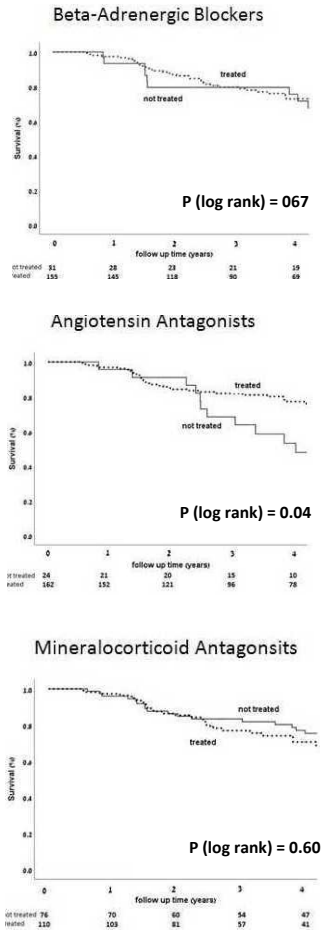

Figure 4: Overall survival KM curves according to presence/absence of ventricular arrhythmia