No impact of mineralocorticoid receptor antagonists on long-term recurrences of ventricular tachyarrhythmias

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[Correction added on 12 January, 2021 after online publication: Tobias Schupp is added as co-corresponding author]

Abstract
Objective: The study sought to assess the prognostic impact of treatment with mineralocorticoid receptor antagonists (MRA) on recurrences of ventricular tachyarrhythmias in implantable cardioverter-defibrillator (ICD) recipients with systolic heart failure (HF).

Background: Data regarding the outcome of patients with ventricular tachyarrhythmias treated with MRA is limited.

Methods: A large retrospective registry was used including consecutive ICD recipients with systolic HF (i.e., left ventricular ejection fraction < 45%) and index episodes of ventricular tachyarrhythmias from 2002 to 2016. Patients treated with MRA were compared to patients without (non-MRA). Kaplan–Meier and multivariable Cox regression analyses were applied for the evaluation of the primary endpoint defined as first recurrence of ventricular tachyarrhythmias at five years. Secondary endpoints were appropriate ICD therapies, first cardiac rehospitalization, and all-cause mortality.

Results: 366 ICD recipients with systolic HF were included, 20% treated with MRA (spironolactone: 65%; eplerenone: 35%) and 80% without. At five years, treatment with MRA was not associated with the primary endpoint of first recurrence of ventricular tachyarrhythmias [47% vs. 48%, log-rank p = 0.732; hazard ratio (HR) = 1.067; 95% confidence interval (CI) 0.736–1.546; p = 0.732]. Accordingly, risk of first appropriate ICD therapies, first cardiac rehospitalization, and all-cause mortality were not affected by the presence of MRA therapy. Finally, patients with spironolactone and eplerenone had comparable risk of first recurrences of ventricular tachyarrhythmias (50% vs. 45%; p = 0.255; HR = 2.263; 95% CI 0.495–10.341; p = 0.292).

Conclusion: Treatment with MRA was not associated with recurrences of ventricular tachyarrhythmias and ICD therapies at five years.

Keywords
eplerenone, heart failure, ICD, mineralocorticoid receptor antagonists, mortality, spironolactone, ventricular fibrillation, ventricular tachycardia

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Systolic heart failure (HF) is one of the most common risk factors for cardiac death and sudden cardiac death (SCD). Therapeutic strategies in patients with systolic HF include an optimal pharmacotherapy, revascularization of significant coronary artery disease (CAD) as well as supply with an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT). HF medication includes angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, and mineralocorticoid receptor antagonists (MRA). They were shown to reduce both all-cause mortality and risk of SCD.

Thus, improved mortality due to eplerenone therapy was demonstrated in patients with acute myocardial infarction (AMI) and left ventricular ejection fraction (LVEF) ≤ 40%. In the "Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study" (EPHESUS), eplerenone revealed a reduction of all-cause mortality by 31% at 30 days of follow-up compared to placebo therapy. MRA treatment may also affect the risk of ventricular tachyarrhythmias by triggering hyperkalemia, especially when prescribed in combination with ACEi/ARB. However, recent studies demonstrated that MRA may decrease the risk of SCD in patients with systolic HF, whereas risk of ventricular tachyarrhythmias was not investigated. Furthermore, patients were usually not stratified by the presence or absence of an ICD. Notably, there is only few data available whether MRA affects the risk of recurrent ventricular tachyarrhythmias in patients with systolic HF and prior ventricular tachyarrhythmias.

Therefore, this study evaluates the prognostic impact of MRA on the primary endpoint of first recurrences of ventricular tachyarrhythmias at five years, as well as on secondary endpoints (i.e., first appropriate ICD therapy, first cardiac rehospitalization, and all-cause mortality) in ICD recipients with systolic HF surviving index episodes of ventricular tachyarrhythmias. Finally, the impact of spironolactone is directly compared to eplerenone.

2 | METHODS

2.1 | Data collection and documentation

The present study included retrospectively all consecutive ICD recipients surviving index episodes of ventricular tachyarrhythmias on admission from 2002 to 2016 at our institution. All relevant clinical data related to the index event as well as related to recurrences of ventricular tachyarrhythmias and rehospitalizations were documented using patients’ files, daily records, documentation from diagnostic examinations and laboratory values, electrocardiograms (ECG), device recordings, and all further information derived from the electronic hospital information system.

Ventricular tachyarrhythmias comprised ventricular tachycardia (VT) and ventricular fibrillation (VF), as defined by current international guidelines. Sustained VT was defined by duration of at least 30 s or causing hemodynamic collapse within 30 s, non-sustained VT by duration of less than 30 s both with wide QRS complex (≥120 ms) at a rate greater than 100 beats per minute. Ventricular tachyarrhythmias at index were documented by 12-lead ECG, ECG telemonitoring, ICD or in case of unstable course or during resuscitation by external defibrillator monitoring. Documented VF was treated by ICD-related shock or external defibrillation and in case of prolonged instability with additional intravenous antiarrhythmic drugs during cardiopulmonary resuscitation (CPR). Electrical storm (ES) was defined as more than or equal to three episodes of ventricular tachyarrhythmias requiring appropriate device therapy and occurring during a period of 24 h.

Further documented data contained baseline characteristics, prior medical history, prior medical treatment, length of index stay, detailed findings of laboratory values at baseline, data derived from all noninvasive or invasive cardiac diagnostics, and device therapies. These included coronary angiography, electrophysiological examination, prior or newly implanted ICD, pacemakers, or cardiac contractility modulators, which were already implanted at index or at follow-up. Imaging modalities comprised echocardiography or cardiac magnetic resonance imaging.

The following cardiac device types were included in the study: ICD, cardiac resynchronization therapy with defibrillator (CRT-D) and subcutaneous ICD (s-ICD). ICD recipients routinely presented every 3–6 months for device check and unscheduled in case of noticed device interrogations at our clinic. Device settings and programming was performed according to current international guidelines by specialized cardiologist in electrophysiology during routine clinical care. Device recordings were re-evaluated retrospectively by independent cardiologists being blinded to final data analysis.

The present study is derived from an analysis of the "Registry of Malignant Arrhythmias and Sudden Cardiac Death - Influence of Diagnostics and Interventions (RACE-IT)," a single-center registry including consecutive patients presenting with ventricular tachyarrhythmias and aborted cardiac arrest being acutely admitted to the University Medical Center Mannheim (UMM), Germany (clinicaltrials.gov identifier: NCT02982473) from 2002 to 2016. The study was carried out according to the principles of the declaration of Helsinki and was approved by the medical ethics committee II of the Medical Faculty Mannheim, University of Heidelberg, Germany.

2.2 | Inclusion and exclusion criteria

Consecutive ICD recipients with systolic HF were included. All patients had a documented episode of ventricular tachyarrhythmias that defines the index event. All analyzed patients had to survive index hospitalization. Systolic HF was defined as documented LVEF < 45%. Decision to treat patients with MRA was based on the discretion of the cardiologists during routine care according to European guidelines. Patients without an activated ICD and systolic HF, death at index hospitalization were excluded from the present analysis. To guarantee sufficient documentation of recurrent ventricular tachyarrhythmias, patients not presenting for at least one ICD check at follow-up were excluded from the present study.
2.3 | Definition of case and control groups

The case group (MRA group) comprised all patients with MRA at discharge. Both patients treated with spironolactone or eplerenone were included. The control group (non-MRA group) comprised all patients without treatment with MRA at discharge. All other medical therapies apart from MRA were allowed.

2.4 | Primary and secondary endpoints

Follow-up period was set at five years for all outcomes. The primary prognostic endpoint was the first recurrence of ventricular tachyarrhythmias (VT or VF) as documented within ICD protocols. Secondary endpoints were overall recurrences at follow-up, recurrences per patient, associated appropriate or inappropriate device therapies (first, overall, per patient), first cardiac rehospitalization, and all-cause mortality at follow-up. Risk of recurrent ventricular tachyarrhythmias was investigated separately for patients with index episodes of non-sustained VT and sustained ventricular tachyarrhythmias (i.e., sustained VT, VF). Further stratification was performed into subgroups of LVEF ≥ 35% and LVEF < 35%, as well as in patients with an optimal HF therapy (i.e., ACEi/ARB therapy and beta-blocker therapy).

Appropriate device therapy was defined as device-related therapy in the presence of VT or VF including antitachycardia pacing (ATP), ICD shock, or both ATP and shock. Inappropriate device therapy was defined as ATP or ICD shock in the absence of VT or VF. First rehospitalization comprised rehospitalizations due to VT, VF, AMI, acute HF, and inappropriate device therapy.

All-cause mortality was documented using our electronic hospital information system and by directly contacting state resident registration offices (bureau of mortality statistics) all across Germany. Identification of patients was verified by place of name, surname, day of birth, and registered living addresses.

2.5 | Statistical methods

Quantitative data are presented as mean ± standard error of the mean (SEM), median and interquartile range, and ranges depending on the distribution of the data and were compared using the Student’s t test for normally distributed data or the Mann–Whitney U test for nonparametric data. Deviations from a Gaussian distribution were tested by the Kolmogorov–Smirnov test. Spearman’s rank correlation for nonparametric data was used to test univariate correlations. Qualitative data are presented as absolute and relative frequencies and compared using the Chi² test or the Fisher’s exact test, as appropriate.

Firstly, univariable Kaplan–Meier method was applied to evaluate prognostic differences within the entire cohort. Hazard ratios (HR) are given together with 95% confidence intervals (CI). The Kaplan–Meier method was applied in the entire study cohort, in the subgroups of LVEF ≥ 35% and < 35%. Then, the impact of MRA therapy was evaluated in patients on optimal HF therapy with ACEi/ARB therapy and additional beta-blocker. Finally, spironolactone was directly compared to eplerenone therapy.

Secondly, multivariable Cox regression models were developed using the “forward selection” option. Predefined variables being used for multivariable Cox regressions included age, chronic kidney disease, prior HF, diabetes mellitus, atrial fibrillation, CAD, LVEF < 35%, treatment with ACEi/ARB, loop diuretics, digitalis, and MRA treatment. Cox regression analyses were applied for the endpoint first recurrence of ventricular tachyarrhythmia and first appropriate ICD therapy. Patients without complete follow-up were censored (accepted lost-to-follow-up rate < 10%).

The result of a statistical test was considered significant for \( p < 0.05 \), a statistical trend was defined as \( p < 0.10 \). SAS, release 9.4 (SAS Institute Inc.) and SPSS (Version 25, IBM) were used for statistics.

3 | RESULTS

3.1 | Study population

A total of 366 consecutive ICD recipients with systolic HF (i.e., LVEF < 45%) were included. All patients survived an index episode of ventricular tachyarrhythmias and were discharged with or without MRA (non-MRA 80% vs. MRA 20%; \( p = 0.0001 \)). Target dosages of MRA were reached already at discharge, as seen for spironolactone in 65% (mean dosage 32 mg/day) and for eplerenone in 35% (mean dosage 26 mg/day). (Table 1).

As seen in Table 1, the median age was 66 years and most patients were males in both subgroups (79%–84%). VT was more common than VF (76%–83% vs. 17%–24%) at index in both treatment groups. The rates of VT and VF in patients with and without MRA were similar (\( p = 0.238 \)). Cardiovascular risk factors (i.e., arterial hypertension, diabetes mellitus, hyperlipidaemia, smoking, and cardiac family history) were equally distributed in both groups (\( p \geq 0.175 \)). A higher rate of atrial fibrillation was observed in patients on MRA treatment (49% vs. 32%; \( p = 0.006 \)). Besides prior HF rates, cardiovascular diseases were similarly distributed between both groups. Further comorbidities, especially rates of chronic kidney disease, AMI, non-iscemic cardiomyopathy, as well as cardiopulmonary resuscitation (CRP) were comparable in patients with and without MRA therapy (\( p \geq 0.080 \)).

Especially ECG intervals, extend of CAD, and degree of LVEF were similar in both groups (\( p \geq 0.051 \); Table 1). Table 2 displays supply with important cardiovascular pharmacotherapies. Most patients were treated with beta-blockers in both subgroups (94%–95%), followed by ACE inhibitors (77% vs. 71%). Comparable daily dosages of beta-blockers and most ACEi/ARB were observed in patients with and without MRA therapy, except for a higher daily dosages of enalapril in patients treated with MRA. Furthermore, more patients in the MRA group were treated with loop diuretics (73% vs. 48%; \( p = 0.001 \)). Accordingly, a higher proportion of patients in the MRA group were treated with digitalis.

Table 3 outlines ICD-related data of the study population. Most patients had an activated transvenous ICD (81%–92%), whereas a
| Characteristic                                                                 | Non-MRA (n = 291; 80%) | MRA (n = 75; 20%) | p-value |
|-----------------------------------------------------------------------------|------------------------|-------------------|---------|
| Age, median (range)                                                         | 66 (22–88)             | 67 (27–83)        | 0.777   |
| Male gender, n (%)                                                          | 243 (84)               | 59 (79)           | 0.325   |
| Ventricular tachyarrhythmia at index, n (%)                                 |                        |                   |         |
| VT                                                                          | 222 (76)               | 62 (83)           | 0.238   |
| VF                                                                          | 69 (24)                | 13 (17)           |         |
| Cardiovascular risk factors, n (%)                                          |                        |                   |         |
| Arterial hypertension                                                       | 191 (66)               | 49 (65)           | 0.961   |
| Diabetes mellitus                                                           | 82 (28)                | 19 (25)           | 0.623   |
| Hyperlipidemia                                                              | 138 (47)               | 29 (39)           | 0.175   |
| Smoking                                                                     | 90 (31)                | 21 (28)           | 0.623   |
| Cardiac family history                                                      | 39 (13)                | 14 (19)           | 0.248   |
| Comorbidities at index stay, n (%)                                          |                        |                   |         |
| Prior myocardial infarction                                                 | 140 (48)               | 29 (39)           | 0.144   |
| Prior CAD                                                                   | 197 (68)               | 42 (56)           | 0.058   |
| Prior PCI                                                                   | 103 (35)               | 22 (29)           | 0.324   |
| Prior HF                                                                    | 134 (46)               | 48 (64)           | 0.006   |
| Atrial fibrillation                                                         | 94 (32)                | 37 (49)           | 0.006   |
| Cardiogenic shock                                                           | 26 (9)                 | 6 (8)             | 0.798   |
| Nonischemic cardiomyopathy                                                  | 41 (14)                | 15 (20)           | 0.205   |
| CPR                                                                         | 53 (18)                | 9 (12)            | 0.080   |
| Chronic kidney disease                                                      | 134 (47)               | 36 (48)           | 0.820   |
| Coronary angiography, n (%)                                                 | 206 (71)               | 40 (53)           | 0.004   |
| No evidence of CAD                                                           | 45 (22)                | 13 (32)           | 0.316   |
| 1-vessel disease                                                            | 46 (22)                | 8 (20)            |         |
| 2-vessel disease                                                            | 43 (21)                | 10 (25)           |         |
| 3-vessel disease                                                            | 72 (35)                | 9 (23)            |         |
| Chronic total occlusion                                                     | 64 (22)                | 14 (19)           | 0.522   |
| Presence of CABG                                                            | 56 (27)                | 7 (18)            | 0.199   |
| AMI                                                                         | 39 (13)                | 10 (13)           | 0.988   |
| STEMI                                                                        | 6 (2)                  | 2 (3)             | 0.749   |
| NSTEMI                                                                       | 33 (11)                | 8 (11)            | 0.869   |
| Target lesions, n (%)                                                       |                        |                   |         |
| Left main trunk                                                             | 1 (3)                  | 1 (10)            | 0.370   |
| Left anterior descending                                                     | 16 (41)                | 4 (40)            | 0.953   |
| Left circumflex                                                             | 8 (21)                 | 3 (30)            | 0.521   |
| Right coronary artery                                                       | 14 (36)                | 2 (20)            | 0.117   |
| Ramus intermedius                                                           | 0 (0)                  | 0 (0)             | –       |
| Bypass graft                                                                | 0 (0)                  | 0 (0)             | –       |
| ECG intervals (mean ± SEM)                                                  |                        |                   |         |
| PQ                                                                          | 181 ± 5                | 169 ± 12          | 0.327   |
| QRS                                                                         | 115 ± 5                | 110 ± 11          | 0.655   |
| QT                                                                          | 408 ± 5                | 421 ± 8           | 0.245   |
| Laboratory data (mean ± SEM)                                                |                        |                   |         |
| Serum/ plasma potassium (mmol/l)                                            | 4.30 ± 0.03            | 4.29 ± 0.07       | 0.967   |

(Continues)
TABLE 1 (Continued)

| Characteristic | Non-MRA (n = 291; 80%) | MRA (n = 75; 20%) | p-value |
|----------------|------------------------|-------------------|---------|
| Glomerular filtration rate (ml/min) | 61.02 ± 1.41 | 60.46 ± 2.31 | 0.235 |
| LVEF (%), (mean ± SEM) | | | |
| LVEF 44%–35% | 93 (32) | 16 (21) | 0.073 |
| LVEF < 35% | 198 (68) | 59 (79) | |

Bold type indicates $p < 0.05$.

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; PCI, percutaneous coronary intervention; SEM, standard error of the mean; VF, ventricular fibrillation; VT, ventricular tachycardia.

minor part of patients had a transvenous CRT-D or s-ICD (1%–17%). ICD were mostly implanted for secondary prevention in patients without MRA (56% vs. 44%; $p = 0.039$), whereas most patients with MRA had an ICD for primary prevention (57% vs. 43%; $p = 0.039$). The median detection thresholds for VT (167 bpm) and for VF (214 bpm) were comparable in both groups, as well as the median cycle length of VT ranging from 320 to 333 ms (Table 3).

3.2 Primary and secondary endpoints

At 5 years of follow-up, freedom from first recurrences of ventricular tachyarrhythmias was comparable in patients with and without MRA therapy (47% vs. 48%, log-rank $p = 0.732$; HR = 1.067; 95% CI 0.736–1.546; $p = 0.732$; Table 3 and Figure 1). The risk first recurrences of ventricular tachyarrhythmias was not affected by MRA treatment irrespective of patients with index episodes of non-sustained VT (47% vs. 44%, log-rank $p = 0.352$; HR = 1.326; 95% CI 0.731–2.406; $p = 0.354$) and sustained ventricular tachyarrhythmias (46% vs. 50%, log-rank $p = 0.849$; HR = 0.954; 95% CI 0.590–1.543; $p = 0.849$) (not shown). Focusing on the entire study cohort, similar rates of first recurrence of sustained VT (32% vs. 32%; $p = 0.995$), non-sustained VT (10% vs. 8%; $p = 0.606$) and VF (6% vs. 7%; $p = 0.789$) were observed in both groups (Table 3). Accordingly, freedom from first appropriate ICD therapy was similar in patients with and without MRA (40% vs. 39%, log-rank $p = 0.590$; HR = 1.117; 95% CI 0.747–1.671; $p = 0.590$).
TABLE 2  Types and dosages of pharmacological therapies

| Characteristic | Non-MRA (n = 291; 80%) | MRA (n = 75; 20%) | p-value |
|----------------|------------------------|-------------------|---------|
| Study drugs; n (%); mg/day (mean ± SEM) | | | |
| MRA – | | 75 (100) | |
| Spironolactone – | | 49 (65) | – |
| – | | 32.03 ± 2.4 | – |
| Eplerenone – | | 26 (35) | – |
| – | | 26.04 ± 1.7 | – |
| Beta-blockers | 272 (94) | 71 (95) | 0.704 |
| Metoprolol | 143 (53) | 34 (48) | 0.482 |
| | 74.93 ± 2.6 | 88.75 ± 6.7 | 0.483 |
| Carvedilol | 78 (29) | 27 (38) | 0.128 |
| | 19.79 ± 1.6 | 20.09 ± 2.7 | 0.825 |
| Bisoprolol | 29 (11) | 8 (11) | 0.883 |
| | 5.85 ± 0.6 | 4.84 ± 1.0 | 0.386 |
| Nebivolol | 12 (4) | 2 (3) | 0.545 |
| | 4.27 ± 0.7 | 5.0 ± 0.0 | 0.142 |
| Sotalol | 10 (4) | 0 (0) | – |
| | 192.00 ± 17.7 | – | – |
| ACEi | 223 (77) | 53 (71) | 0.285 |
| Ramipril | 123 (55) | 38 (72) | 0.028 |
| | 5.70 ± 0.3 | 5.46 ± 0.5 | 0.429 |
| Lisinopril | 13 (6) | 2 (4) | 0.553 |
| | 18.54 ± 4.4 | 10.00 ± 0.0 | 0.020 |
| Enalapril | 71 (32) | 11 (21) | 0.112 |
| | 12.80 ± 1.0 | 17.27 ± 4.2 | 0.004 |
| Others | 16 (7) | 2 (4) | 0.367 |
| ARB | 34 (12) | 16 (22) | 0.034 |
| Candesartan | 20 (63) | 11 (69) | 0.500 |
| | 13.00 ± 2.1 | 14.80 ± 2.2 | 0.524 |
| Valsartan | 1 (3) | 1 (6) | 0.542 |
| | 160.00 ± 0.0 | 40.00 ± 0.0 | – |
| Irbesartan | 2 (6) | 1 (6) | 1.000 |
| | 300.00 ± 0.0 | 150.00 ± 0.0 | – |
| Others | 11 (32) | 3 (19) | 0.318 |
| Loop diuretics | 139 (48) | 55 (73) | 0.001 |
| Torasemide | 119 (86) | 45 (82) | 0.510 |
| | 15.02 ± 1.7 | 14.89 ± 2.6 | 0.929 |
| Furosemide | 20 (14) | 10 (18) | 0.510 |
| | 94.7 ± 37.1 | 141.75 ± 68.8 | 0.439 |
| Thiazide diuretics | 71 (24) | 18 (24) | 0.943 |
| Hydrochlorothiazide | 71 (100) | 17 (94) | 0.202 |
| | 19.24 ± 1.1 | 19.32 ± 2.0 | 0.480 |
| Xipamide | 0 (0) | 1 (6) | 0.202 |

(Continues)
TABLE 2  (Continued)

| Characteristic | Non-MRA (n = 291; 80%) | MRA (n = 75; 20%) | p-value |
|----------------|-----------------------|-------------------|---------|
|                |                       |                   |         |
|                | 10.00 ± 0.0           |                   |         |
| Digitalis      | 68 (23)               | 27 (36)           | 0.026   |
| Digoxin        | 45 (66)               | 19 (70)           | 0.694   |
| Digitoxin      | 0.14 ± 0.0            | 0.14 ± 0.0        | 0.449   |
| Amiodarone     | 23 (34)               | 8 (30)            | 0.694   |
|                | 0.08 ± 0.0            | 0.08 ± 0.0        | 0.396   |
|                | 200.00 ± 3.6          | 200.00 ± 0.0      | 0.374   |

Bold type indicates \( p < 0.05 \).
Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

**FIGURE 2**  Freedom from first appropriate (left) and inappropriate implantable cardioverter-defibrillator therapies (right) comparing patients with and without MRA therapy [Color figure can be viewed at wileyonlinelibrary.com]

(Figure 2, left panel). No difference was found for inappropriate ICD therapies (16% vs. 12%; \( p = 0.359; HR = 1.496; 95\% CI 0.775–2.887; p = 0.230 \) (Figure 2, right panel).

Even after stratification by LVEF 44%–35% and LVEF < 35%, no impact of MRA compared to non-MRA treatment was found (Figure 3).

Furthermore, MRA patients revealed comparable rates of overall first rehospitalization (35% vs. 31%), mainly being attributed to VT recurrences in both groups (16% vs. 19%), as well as similar rate of all-cause mortality at five years (35% vs. 24%; \( p = 0.054 \); Table 3).

### 3.3 Patients with optimal HF therapy

There were 307 patients with optimal pharmacotherapy including ACE inhibitor/ARB plus beta-blockers (MRA: 22%; non-MRA: 78%). In these patients, no impact of MRA treatment regarding the primary endpoint of first recurrence of ventricular tachyarrhythmias was found (46% vs. 47%; log rank \( p = 0.713 \)) (not shown). Furthermore, no impact was found regarding the risk of appropriate ICD therapies (38% vs. 37%; log rank \( p = 0.557 \)) (not shown).

### 3.4 Multivariable Cox regression models

After multivariable adjustment, MRA treatment was not associated with the risk of first recurrence of ventricular tachyarrhythmias at five years (HR = 0.966; 95% CI 0.653–1.429; \( p = 0.862 \); Table 4). Accordingly, MRA patients were not associated with risk of appropriate ICD therapy (HR = 1.046; 95% CI 0.682–1.603; \( p = 0.979 \); Table 4). In contrast, especially CAD was associated with decreased risk of first recurrence of ventricular tachyarrhythmias (HR = 0.675) and appropriate ICD therapies (HR = 0.688).
## TABLE 3  ICD data and primary and secondary endpoints

| Characteristic                              | Non-MRA (n = 291; 80%) | MRA (n = 75; 20%) | p-value |
|---------------------------------------------|------------------------|-------------------|---------|
| **Type of ICD, n (%)**                      |                        |                   |         |
| ICD                                         | 267 (92)              | 61 (81)           | 0.019   |
| CRT-D                                       | 20 (7)                | 13 (17)           |         |
| s-ICD                                       | 4 (1)                 | 1 (1)             |         |
| **Implant indication, n (%)**               |                        |                   |         |
| Primary prevention                          | 128 (44)              | 43 (57)           | 0.039   |
| Secondary prevention                        | 163 (56)              | 32 (43)           |         |
| **ICD programming, bpm, median (interquartile range)** |                |                   |         |
| VT detection threshold                      | 167 (151–171)         | 167 (162–171)     | 0.371   |
| VF detection threshold                      | 214 (214–220)         | 214 (214–214)     | 0.311   |
| **Primary endpoint**                        |                        |                   |         |
| First recurrence ventricular tachyarrhythmias, n (%) |              |                   |         |
| Overall                                     | 139 (48)              | 35 (47)           | 0.865   |
| Non-sustained VT                            | 29 (10)               | 6 (8)             | 0.606   |
| Sustained VT                                | 93 (32)               | 24 (32)           | 0.995   |
| VF                                          | 17 (6)                | 5 (7)             | 0.789   |
| ES                                          | 20 (7)                | 8 (11)            | 0.270   |
| **Secondary endpoints**                     |                        |                   |         |
| Overall recurrences at follow-up, n (%)     |                        |                   |         |
| Non-sustained VT                            | 56 (19)               | 14 (19)           | 0.910   |
| Sustained VT                                | 111 (38)              | 27 (36)           | 0.733   |
| VF                                          | 32 (11)               | 8 (11)            | 0.935   |
| ES                                          | 20 (7)                | 8 (11)            | 0.270   |
| VT cycle length, ms, mean ± SEM             | 320 ± 6               | 333 ± 14          | 0.320   |
| Recurrences per patient, mean ± SEM         |                        |                   |         |
| Non-sustained VT                            | 7.5 ± 2.8             | 3.3 ± 1.9         | 0.466   |
| Sustained VT                                | 6.1 ± 1.3             | 10.3 ± 4.9        | 0.237   |
| VF                                          | 0.4 ± 0.1             | 0.3 ± 0.1         | 0.625   |
| ES                                          | 0.1 ± 0.0             | 0.1 ± 0.1         | 0.311   |
| **First device therapies, n (%)**           |                        |                   |         |
| Overall appropriate device therapy          | 114 (39)              | 30 (40)           | 0.896   |
| Appropriate shock                           | 41 (14)               | 15 (20)           | 0.205   |
| Appropriate ATP only                        | 73 (25)               | 15 (20)           | 0.358   |
| Overall device therapies at follow-up, n (%)|                        |                   |         |
| Overall appropriate device therapy          | 114 (39)              | 30 (40)           | 0.896   |
| Appropriate shock                           | 61 (21)               | 22 (29)           | 0.123   |
| Appropriate ATP only                        | 94 (32)               | 25 (33)           | 0.865   |
| Inappropriate device therapy                | 35 (12)               | 12 (16)           | 0.359   |
| Device therapies per patient, mean ± SEM    |                        |                   |         |
| Appropriate shock                           | 3.8 ± 0.2             | 2.3 ± 0.3         | 0.928   |
| Appropriate ATP only                        | 4.7 ± 1.0             | 9.5 ± 5.0         | 0.138   |

(Continues)
TABLE 3 (Continued)

| Characteristic                      | Non-MRA (n = 291; 80%) | MRA (n = 75; 20%) | p-value |
|-------------------------------------|------------------------|-------------------|---------|
| Inappropriate device therapy        | 0.3 ± 0.1              | 0.2 ± 0.1         | 0.736   |
| First rehospitalization, n (%)      |                        |                   |         |
| Overall                             | 91 (31)                | 26 (35)           | 0.574   |
| VT                                  | 28 (19)                | 12 (16)           | 0.114   |
| VF                                  | 6 (2)                  | 2 (3)             | 0.749   |
| AMI                                 | 4 (1)                  | 1 (1)             | 0.978   |
| Acute HF                            | 26 (9)                 | 6 (8)             | 0.798   |
| Inappropriate device therapy        | 13 (5)                 | 3 (4)             | 0.860   |
| Other                               | 14 (5)                 | 2 (3)             | 0.418   |
| All-cause mortality, at 5 years, n | 69 (24)                | 26 (35)           | 0.054   |

Bold type indicates p < 0.05.

Abbreviations: ATP, anti-tachycardia pacing; CRT-D, cardiac resynchronization therapy with defibrillator; ES, electrical storm; ICD, implantable cardioverter-defibrillator; s-ICD, subcutaneous ICD.

3.5 Comparison of spironolactone versus eplerenone

Finally, the impact of eplerenone was compared to spironolactone, whereas similar risk of recurrences of ventricular tachyarrhythmias was found (50% vs. 45%; p = 0.255; HR = 2.263; 95% CI 0.495–10.341; p = 0.292; Figure 4).

4 DISCUSSION

The present study evaluates the prognostic impact of MRA treatment on the primary endpoint of recurrences of ventricular tachyarrhythmias, as well as on secondary endpoints, such as appropriate ICD therapies, first cardiac rehospitalization, and all-cause mortality at 5 years of follow-up in ICD recipients with systolic HF with LVEF < 45% surviving index episodes of ventricular tachyarrhythmias. This data suggests no impact of MRA therapy on the risk of recurrent ventricular tachyarrhythmias and appropriate ICD therapies. Especially in patients with optimal HF therapy (i.e., beta-blocker plus ACE inhibitor/ARB), no impact of MRA therapy was found. Furthermore, risk of first cardiac rehospitalization and all-cause mortality were comparable regarding patients with and without MRA therapy. Finally, risk of recurrent ventricular tachyarrhythmias did not differ among patients treated with spironolactone or eplerenone.
TABLE 4  Multivariable Cox regression analyses

| Endpoint                      | HR   | 95% CI          | p-value |
|-------------------------------|------|-----------------|---------|
| Recurrence of VT/VF           |      |                 |         |
| Age                           | 1.013| 0.997–1.028     | 0.106   |
| Diabetes                      | 0.766| 0.536–1.095     | 0.144   |
| Chronic kidney disease        | 1.197| 0.876–1.636     | 0.159   |
| Prior HF                      | 0.962| 0.704–1.313     | 0.807   |
| Atrial fibrillation           | 1.240| 0.900–1.710     | 0.188   |
| CAD                           | 0.675| 0.475–0.959     | 0.028   |
| LVEF < 35%                    | 1.074| 0.759–1.520     | 0.687   |
| ACEi/ARB                      | 0.671| 0.429–1.049     | 0.080   |
| Loop diuretics                | 1.039| 0.741–1.456     | 0.825   |
| Digitalis                     | 1.237| 0.881–1.738     | 0.219   |
| MRA                           | 0.966| 0.653–1.429     | 0.862   |

| Appropriate ICD therapy       |      |                 |         |
| Age                           | 1.020| 1.003–1.037     | 0.020   |
| Diabetes                      | 0.689| 0.461–1.029     | 0.069   |
| Chronic kidney disease        | 1.200| 0.852–1.691     | 0.298   |
| Prior HF                      | 1.013| 0.720–1.423     | 0.943   |
| Atrial fibrillation           | 1.047| 0.733–1.494     | 0.802   |
| CAD                           | 0.688| 0.470–1.008     | 0.055   |
| LVEF < 35%                    | 1.098| 0.748–1.612     | 0.634   |
| ACEi/ARB                      | 0.496| 0.314–0.782     | 0.003   |
| Loop diuretics                | 0.959| 0.662–1.390     | 0.825   |
| Digitalis                     | 1.407| 0.977–2.025     | 0.066   |
| MRA                           | 1.046| 0.682–1.603     | 0.837   |

Bold type indicates statistical significance.
Level of significance: p < 0.05.
Abbreviations: CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Besides increasing the risk of mortality, systolic HF represents one of the most common reasons for increasing the risk of ventricular tachyarrhythmias leading to appropriate device therapies. Precription of MRA was postulated to decrease the risk of ventricular tachyarrhythmias leading to SCD in various studies. A reduction of SCD by 21% was demonstrated in a recent meta-analysis including seven trials and more than 8,000 patients. Moreover, MRA therapy reduced the risk of ventricular premature complexes and VT. These findings are in contrast with the present study that demonstrated that especially episodes of VT were equally distributed between both groups.

In contrast, the antiarrhythmic effect of MRA treatment was investigated in few studies with rather small sample sizes. A study by Wase et al. retrospectively included 64 patients with an ICD with LVEF < 35%. At 12 months of follow-up, patients treated with spironolactone had a lower incidence of VT requiring ATP. In contrast, occurrence of nonsustained VT and VF were not affected by treatment with spironolactone. This study confirms their findings regarding the occurrence of non-sustained VT and VF, but did not observe differences regarding the occurrence of sustained VT at 5 years.

In line, the “SPironolactone to Reduce ICD Therapy” (SPIRIT) trial investigated the impact of spironolactone in ICD recipients. A total of 90 patients were randomized to receive spironolactone or placebo therapy. After a median follow-up of 35 months, spironolactone was not associated with decreased risk of recurrent ventricular tachyarrhythmias. In contrast to the present study, patients in the SPIRIT trial were not candidates for guideline recommended spironolactonetherapy.

However, the decision to treat patients with MRA may also depend on the severity of HF symptoms [i.e., New York Heart Association (NYHA) class]. A meta-analysis including data from the MADIT II and SCD-HeFT trials with more than 1,400 patients with an ICD demonstrated that especially lower LVEF, higher NYHA class, and the absence of beta-blocker therapy were associated with increased risk of appropriate ICD shock in patients with systolic HF. Thus, MRA may more likely prescribed for patients with higher NYHA class and severe cardiac diseases. That MRA treatment may be more common...
in patients with severe heart disease with increasing risk of ventricular tachyarrhythmias is supported by an increased supply with digitalis (36% vs. 23%) in patients with MRA therapy in the present study. To re-evaluate the prognostic impact of MRA therapy in more homogenous subgroups, additional subanalyses were performed, and patients were stratified by LVEF and the presence of an optimal HF medication (i.e., ACE inhibitor/ARB plus beta-blocker). Consistency was proven suggesting no additional impact of MRA therapy in any of the analyzed subgroups.

Furthermore, there are heterogeneous findings regarding the impact of MRA therapy on rehospitalization. For instance, a retrospective study investigated the impact of MRA therapy in more than 8,000 patients with acute coronary syndromes. After a median follow-up of 40 months, MRA was not associated with a reduction of HF-related rehospitalizations and cardiovascular mortality. This study confirms these findings including a different subgroup of patients with ventricular tachyarrhythmias and ICD.

Finally, MRA therapy may increase serum potassium levels and therefore decrease the risk of appropriate ICD therapies, ventricular tachyarrhythmias, and SCD. It was recently demonstrated that especially hypokalemia, but not hyperkalemia was associated with increased risk of appropriate ICD therapies within a subset of this registry. In line, especially hyperkalemia was shown to be the most common reason to discontinue MRA therapy. Notably, discontinuation of MRA treatment may further increase all-cause mortality, cardiovascular mortality, and hospitalizations due to acute HF. Increasing serum potassium levels due to initiation of MRA therapy is mostly treated with discontinuation (47%) rather than decreasing MRA dosages (10%). Different strategies to prevent hyperkalemia due to MRA therapy consist of reducing dosage of ACEi/ARB therapy.

However, in the present study, supply with ACEi/ARB did not differ between patients with or without MRA therapy (93% vs. 89%). Except for daily dosage of lisonipril, ACEi/ARB dosage was not reduced in patients treated with MRA.

In conclusion, this study does not identify MRA therapy to decrease the risk of recurrent ventricular tachyarrhythmias and appropriate ICD therapies in patients with systolic HF with LVEF < 45%. Finally, no impact of MRA therapy was found regarding the risk of first appropriate ICD therapies, first cardiac rehospitalization, and all-cause mortality at 5 years. Further studies are necessary to separate the interaction of MRA therapy and severity of underlying heart disease in patients with systolic HF.

4.1 Study limitations

The main limitation of the study consists in the retrospective study design and the rather small sample size. Pharmacological therapies were based on discharge medication at index event. Choice to treat patients with or without MRA was made by physicians during routine clinical care, but in accordance with current European guidelines. Discontinuation of MRA therapy was not assessed for the present study. Unmeasured confounding, especially due to inhomogeneous distribution of severity of cardiac disease (such as HF symptoms [i.e., NYHA class], ischemia-related scar burden, and further substrates for ventricular tachyarrhythmias) cannot be excluded. Echocardiographic values besides LVEF, such as ventricular dimensions and hypertrophy, were only available in minor part of the patients were therefore not included in this study. Furthermore, rehospitalization was only assessed at one institution only. To minimize lost to follow-up rate, all patients not meeting ICD follow-up for at least once after discharge were excluded from present analysis.

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AUTHOR CONTRIBUTIONS

Tobias Schupp and Ibrahim Akin substantially contributed to the conception and design of the work, data acquisition and analysis as well as interpretation of data for the work, drafted the work, and revisited for critically important intellectual content. Linda Reiser, Armin Bollow, Gabriel Taton, Martin Borggrefe, Thomas Reichelt, Dominik Ellguth, Niko Engelke, Max Barre, Julian Müller, Kathrin Weidner, Seung-Hyun Kim, Muharrem Akin, and Dirk Große Meininghaus substantially contributed to data acquisition and analysis as well as interpretation of data for the work and revisited for critically important intellectual content. Michael Behnes conceived the study, substantially contributed to the conception and design of the work, data acquisition and analysis as well as interpretation of data for the work, drafted the work, and revisited for critically important intellectual content. All authors read and approved the final manuscript.
CONFLICTS OF INTEREST
The authors declare that they do not have any conflicts of interest.

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