Reduction of ventricular tachyarrhythmia by treatment of atrial fibrillation in ICD patients with dual-chamber implantable cardioverter/defibrillators capable of atrial therapy delivery: the REVERT-AF Study

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Aims The purpose of this prospective, randomized, multicentre study was to investigate whether the incidence of ventricular tachyarrhythmia can be reduced in standard implantable cardioverter/defibrillator (ICD) patients by implanting a dual-chamber ICD capable of atrial therapy delivery.

Methods and results A Jewel AF or GEM III AT ICD (Medtronic Inc., Minneapolis, MN, USA) was implanted in 122 patients (62.3 ± 10.5 years; 84.4% male; coronary artery disease 71.3%; left ventricular ejection fraction 39.7 ± 13.6%; secondary ICD indication 91%). Overall, 31.2% of the patients had paroxysmal atrial fibrillation (AF)/atrial tachycardia (AT) before ICD implantation (n = 38). Implantable cardioverter/defibrillator therapies for AT/AF were activated and de-activated every 3 months in a cross-over study design. The mean follow-up was 18.5 ± 7.7 months (6.29 ± 2.2 cross-over/patient). Overall, there were 684 episodes of ventricular tachyarrhythmias in 48.4% of patients (n = 59). In 33.6% of patients (n = 41), 532 supraventricular tachyarrhythmias occurred. Activation of ICD therapies for AT/AF did not result in a reduction of ventricular tachyarrhythmias (P = 0.92). Patients with monomorphic ventricular tachycardias (mVTs) as index arrhythmia for ICD implantation or inducible mVTs in the electrophysiological study had the highest probability of recurrences of ventricular tachyarrhythmias.

Conclusion For patients with standard indications for ICD therapy and no indication for cardiac pacing, a dual-chamber ICD capable of atrial tachyarrhythmia treatment offers no benefit concerning a reduction of ventricular tachyarrhythmias.

KEYWORDS Implantable cardioverter/defibrillator; Capability of atrial therapy; Recurrence rate of ventricular tachyarrhythmia

Introduction

Atrial fibrillation (AF) is associated with an independent adverse prognosis in patients with advancing age and structural heart disease.1,2 Therefore, it is not surprising that atrial tachyarrhythmias, including AF and atrial tachycardia/flutter (AT), are common in patients with implantable cardioverter/defibrillators (ICD).3,4 The AVID trial showed that AF was an independent predictor of mortality in ICD patients.5 Moreover, AF is also an independent predictor of appropriate as well as inappropriate device therapy.6 About 20–25% of ICD patients had AF before implantation, and during lifespan of the ICD, up to 50% may develop AF.7 There are at least two pathophysiological factors as to how AF can influence the recurrence rate of VT/VF episodes. First, the irregularity of RR cycles can cause short–long–short sequences which are immediately preceding VT/VF episodes. Secondly, AF can cause and be caused by haemodynamic deterioration, which is also a known risk factor for recurrences of
VT/VF episodes. It could be shown that termination of AT/AF significantly delayed the occurrence of VT/VF. The efficacy of dual-chamber ICDs with atrial antitachycardia functions in treating spontaneous atrial tachyarrhythmias in patients with life-threatening VT/VF is described with up to 71% for AT and up to 62% for AF episodes. However, other investigations have reported that the efficacy rates are much lower. In addition, it is well recognized that many episodes of atrial tachyarrhythmias are self-terminated. Therefore, the purpose of this prospective, randomized, multicentre study was to investigate whether the incidence of ventricular tachyarrhythmia can be reduced in standard ICD patients by implanting a dual-chamber ICD capable of AT/AF treatment.

Methods

Study design

This was a prospective, randomized multicentre trial including patients from seven different German ICD centres. Initial activation of the AT/AF therapy variables were randomized at ICD implantation. Thereafter, activation and de-activation of the AT/AF therapy variables was performed every 3 months in a cross-over study design. Programming of the ventricular detection and therapy variables was mainly left to the investigator's discretion.

Patients

The study protocol was approved by the Ethic Committees of the various institutions. A total of 122 patients with an indication for ICD implantation according to American Guidelines for implantation of cardiac pacemakers and anti-arrhythmia devices were included in the study. All patients underwent first ICD implantation. Patients with and without history of paroxysmal AT or AF could be included in the study. Written informed consent was obtained from all patients. Patients with a history of cerebrovascular events, chronic AF, or incomplete revascularization were excluded. Additionally, patients who were dependent on atrial pacing or had previously undergone right ventricular valve replacement were excluded.

Dual-chamber defibrillator: features

The Jewel AF ICD (Model 7250, Medtronic Inc., Minneapolis, MN, USA) was implanted in 40 patients (32.8%), and the Jewel GEM III AT ICD (Model 7276, Medtronic Inc.) was implanted in 82 patients (67.2%). Both ICDs are programmable dual-chamber devices capable of dual chamber pacing (DDD pacing) as well as detection and treatment of atrial and ventricular tachyarrhythmia. The Jewel GEM III AT offers an additional rate response pacing function (DDDR). A dual-chamber algorithm (PR-Logic®) is used to differentiate supraventricular from ventricular tachyarrhythmia on the basis of the ratio and timing of P-waves with respect to R-waves. For ventricular tachyarrhythmias, two detection zones are available. Treatment options include various antitachycardia pacing (ATP) modes, low- and high-energy cardioversion, and defibrillation. The maximum output is 27 J for the Jewel AF ICD and 30 J for the Jewel GEM III AT ICD.

Atrial tachyarrhythmia are detected by a combination of the median atrial cycle length and AT/AF evidence counter that uses the number of sensed atrial events in consecutive RR intervals. The device discriminates AT from AF on the basis of two programmable detection zones, which usually overlap. If the median atrial cycle length is in the overlap zone, the rhythm is classified as AT if the cycle length is regular and AF if the rhythm is irregular. Outside of the overlap zone, the rhythm is classified according to the median atrial cycle length in the AF or AT zone independent of the regularity of the rhythm. Atrial therapies include atrial ATP, high-frequency burst pacing, which is 50 Hz pulse train variable in duration (from 0.5 to 3 s) and in the number of sequences (from 1 to 20), and atrial defibrillation with 27–30 J.

Dual-chamber defibrillator: programming

Concerning the ventricular detection and therapy variables, the ICD device was programmed as a two-zone device. The detection interval of the VT zone was programmed 60–80 ms longer than the slowest documented or induced VT. The PR-Logic algorithm was activated including the AF/AT mode as well as the sinus tachycardia mode. The 'other 1:1 supraventricular tachycardia (SVT)' mode was optional to the investigator's discretion. The SVT limit was programmed to 320 ms. Antitachycardia pacing and shocks were programmed in the VT zone, shocks in the VF zone. The defibrillation energy was programmed 10–15 J above the intraoperatively tested successful defibrillation energy. Programming changes were made during follow-up in patients who had spurious ICD therapies for SVTs.

AT/AF therapy variables were activated according to the randomization protocol. AT/AF detection was programmed 'ON' throughout the total follow-up. If AT/AF therapy variables were activated 3–10 sequences of atrial ATP and 3–10 sequences of atrial 50 Hz burst, about 1–3 s were programmed in the AT zone. In the AF zone, 3–10 sequences of atrial 50 Hz burst about 1–3 s were programmed. Atrial defibrillation therapy in the AT and AF zones was activated if the patient gave consent to atrial shock therapy. Antitachycardia pacing and burst therapies were delivered without any time delay. Atrial shocks were delivered with a time delay of 12 h.

Data analysis and statistics

Each spontaneous tachyarrhythmia episode was reviewed to determine the appropriateness of detection and the efficacy of therapy on the basis of the information from the device memory (intracardiac electrogram, event markers, RR, PP, PR, and RP intervals) and of patient history. The analysis was performed on the basis of an expert panel blinded to the programming of the ICD device. If the experts did not reach a consent, a third expert was asked. On the basis of the uneven number of experts, a decision was reached. The burden of AF/tachycardias was calculated on the basis of the stored AF/AT episodes and the AF/AT counter of the device. Termination of the AF/AT was defined as termination after atrial therapy delivery within the stored EGM strip, knowing well the bias that spontaneous termination of these tachyarrhythmias often occurs. All data were collected in a Microsoft Access 2002 SP3 database. Quantitative analyses were performed using SPSS version 11.5. All data are presented as mean ± SD for continuous variables and frequencies or percentages for discrete variables. In order to investigate the association of the number of episodes with certain covariates, a generalized linear model with log-linear link function and Poisson variance function was set up. Parameter estimation was carried by means of generalized estimating equations (GEE), assuming an autoregressive working correlation matrix. Wald-type significance tests were carried out. Statistical analyses were performed using the SAS (SAS Institute, North Carolina, USA) and S-PLUS software (Mathsoft Inc., Seattle, Washington, USA). A value of P < 0.05 was considered significant.

Results

Patients, implantation, and pacemaker programming

Patient demographics are summarized in Table 1. The 122 patients were enrolled in seven centres. Electrophysiological data of the patients are summarized in Table 2. Overall, 91% of patients were treated with an ICD owing to
an arrhythmic index event, whereas 9% of patients had a primary ICD indication. An electrophysiological (EP) study was performed in 85.2% of patients. Ventricular tachyarrhythmias could be induced in 79.0% of these patients (68.6% of all patients). All patients had sinus rhythm at the time of enrolment. Intermittent AF and AT was documented by at least one ECG strip in 31.2% of the patients before ICD implantation.

A Jewel AF ICD was implanted in 40 patients (32.8%) and a Jewel GEM III AT ICD was implanted in 82 patients (67.2%).

Ventricular arrhythmia

Overall, 532 supraventricular tachyarrhythmias occurred in 33.6% of patients (n = 41). These 532 supraventricular tachyarrhythmias included 150 episodes in the AF zone (28.2%) in 26 patients (21.3% of patients), 230 episodes in the AT zone (43.2%), 43 episodes of other SVTs (8.1%), and 99 episodes of other SVTs (18.4%) in 35 patients (27.9%).

Ventricular arrhythmia

During a mean follow-up of 18.5 ± 7.7 months, 684 episodes of ventricular tachyarrhythmias occurred in 48.4% of patients (n = 59). Only 4.4% of episodes (n = 30) were VF, whereas 95.6% of episodes (n = 654) were monomorphic ventricular tachycardia (mVT) episodes. The sensitivity of the PR-Logic detection algorithm for VT/VF was 100%, with a VT/VF positive predictivity of 76.6%. The mean cycle length of the mVTs was 327 ± 46 ms. All 98 ventricular tachycardia episodes detected in the VF zone were classified correctly and terminated by the ICD device (8% by ATP via the VT/VF discrimination mode, 81% by shock, and 10% terminated spontaneously before shock delivery). All mVT episodes were correctly classified by the ICD system (10.6% in the VF zone; 89.4% in the VT zone). Only nine mVTs were not terminated by the ICD system (1.4% of all mVTs). Most mVTs were treated by ATP (85.9%). Implantable cardioverter/defibrillator shocks terminated 11.8% of all mVTs, and 2.3% of mVTs terminated before therapy delivery.

**Supraventricular arrhythmia**

Overall, 684 supraventricular tachyarrhythmias occurred in 48.4% of patients (n = 59). Only 4.4% of episodes (n = 30) were VF, whereas 95.6% of episodes (n = 654) were monomorphic ventricular tachycardia (mVT) episodes. The sensitivity of the PR-Logic detection algorithm for VT/VF was 100%, with a VT/VF positive predictivity of 76.6%. The mean cycle length of the mVTs was 327 ± 46 ms. All 98 ventricular tachycardia episodes detected in the VF zone were classified correctly and terminated by the ICD device (8% by ATP via the VT/VF discrimination mode, 81% by shock, and 10% terminated spontaneously before shock delivery). All mVT episodes were correctly classified by the ICD system (10.6% in the VF zone; 89.4% in the VT zone). Only nine mVTs were not terminated by the ICD system (1.4% of all mVTs). Most mVTs were treated by ATP (85.9%). Implantable cardioverter/defibrillator shocks terminated 11.8% of all mVTs, and 2.3% of mVTs terminated before therapy delivery.

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109 episodes of sinus tachycardia (20.5%). The recurrence rate of SVTs was statistically not different, depending on the activation of AT/AF therapies ($P = \text{ns}$). The positive predictivity for SVTs was 100%, whereas only 60.7% of all episodes were correctly classified as SVT by the ICD systems (specificity for VT/VF detection). This was based on a wrong classification of AF with rapid ventricular response as VF or VT (23.3% of all AF episodes) as well as a wrong classification of other SVT and sinus tachycardia mainly classified as mVts. Atrial tachycardia/flutter was correctly classified in 90% of all episodes (207/230 episodes), and 72.9% of all episodes in the AF zone could be terminated by the ICD system in 76.7%. Overall, 39.6% of all episodes in the AF zone could be terminated by the ICD system in case of activated AT/AF therapies. AF was correctly diagnosed by the ICD system in 76.7%. Obtained SVTs were statistically not different, depending on the activation of AT/AF therapies ($P = \text{ns}$). The positive predictivity for SVTs was 100%, whereas only 60.7% of all episodes were correctly classified as SVT by the ICD systems (specificity for VT/VF detection). This was based on a wrong classification of AF with rapid ventricular response asVF or VT (23.3% of all AF episodes) as well as a wrong classification of other SVT and sinus tachycardia mainly classified as mVts. Atrial tachycardia/flutter was correctly classified in 90% of all episodes (207/230 episodes), and 72.9% of all episodes in the AT zone could be terminated by the ICD system (ATP and burst therapy) in case of activated AT/AF therapies. AF was correctly diagnosed by the ICD system in 76.7%. Overall, 39.6% of all episodes in the AF zone could be terminated by the ICD system in case of activated AT/AF therapies. However, only three patients with AF/AT episodes accepted activation of shock therapy for SVTs. In these three patients, seven AF episodes occurred, which were all terminated by the ICD shock. The overall AF burden was 1.03 ± 6.05 h/month in case of deactivated AT/AF therapies and 0.91 ± 5.58 h/month in case of activated AF/AT therapies ($P = \text{ns}$). Even in the patients with AF/AT episodes during follow-up, activation of AF/AT therapies did not result in a reduction of the AF/AT burden (3.47 ± 10.83 h/month vs. 3.05 ± 10.04 h/month, $P = 0.22$).

### Reduction and predictability of ventricular arrhythmia recurrences

Activation of ICD therapies for AT/AF did not result in a reduction of ventricular tachyarrhythmia in the overall patient group ($P = 0.92$). The recurrence rate of VT/VF episodes depending on the activation of AT/AF therapies in the last 3 months is summarized in Table 4. Overall, 19.7% of patients ($n = 24$) had both, supraventricular as well as ventricular tachyarrhythmia during follow-up. Even in this special subgroup of patients as well as in patients with paroxysmal AF or AT before ICD implantation, there was no reduction in the recurrence rate of VT/VF by activating AT/AF therapies.

<table>
<thead>
<tr>
<th>Programming last 3 months</th>
<th>Number of VT/VF episodes during the last 3 months</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>AT/AF + VT/VF</td>
<td>311</td>
</tr>
<tr>
<td>Percentage</td>
<td>81.0</td>
</tr>
<tr>
<td>VT/VF only</td>
<td>332</td>
</tr>
<tr>
<td>Percentage</td>
<td>84.9</td>
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FU, Follow-up. The number and percentage of follow-ups according to the number of recurrences of VT/VF episodes within the last 3 months ($x$-axis) are depicted against the programming of the device within the last 3 months ($y$-axis).

### Discussion

The principal finding of this study is that dual chamber ICD capable of atrial tachyarrhythmia treatment offers no benefit concerning the recurrence rate of ventricular arrhythmia in patients with standard indication for ICD therapy. Even in patients with a history of paroxysmal AF/AT or inducible AF/AT during EP study, activation of AT/AF device therapies did not result in a significant reduction of VT/VF episodes during follow-up. The most powerful predictors for VT recurrences were secondary prevention ICD indication, mVT as ventricular index arrhythmia, and inducible mVT during EP testing.

![Figure 1](https://academic.oup.com/europace/article-abstract/9/7/534/552638/537?download=true)

**Figure 1** Predictors of recurrences of ventricular tachyarrhythmia during follow-up (analysis of GEE-estimated values with 95% confidence interval). LV-EF, left ventricular ejection fraction.
The negative results of this study have to be discussed with regard to the detection function of the ICD device for SVT discrimination, the efficacy in termination of AT/AF episodes, as well as reduction of AF/AT burden by the ICD. The primary function of an ICD is to treat life-threatening ventricular tachyarrrhythmia. Therefore, any ICD detection algorithm should reach a VT/VF sensitivity of 100%, which could be shown for the PR-Logic algorithm in several studies of the Worldwide Jewel AF investigators as well as in this study. However, the positive VT/VF predictivity of the PR-Logic algorithm was only 76.6%, which was however within the range of published data for the PR-Logic algorithm. This was mainly caused by misclassification of other SVT and sinus tachycardia as mVTs. This kind of misclassification is a well-known problem of the first generation of the PR-Logic algorithm (e.g. used in the Jewel AF ICD and the Jewel GEM III AT ICD). The positive SVT predictivity of the PR-Logic algorithm was described up to 100%, which could be supported in this study. Therefore, sensitivity, specificity, and positive VT/VF as well as SVT predictivity values obtained in this study were comparable with the results of prior ICD study investigating the PR-Logic algorithm of the Jewel AF ICD and the Jewel GEM III AT ICD.

The efficacy in termination of AT/AF episodes by ICD devices was described with a high range in previous studies. Antitachycardia pacing including 50 Hz burst has a comparatively high success rate in terminating regular supraventricular tachyarrhythmias mostly described as AT. The success rate was described between 45 and 72% of all episodes. In this study, 72.9% of all AT episodes could be terminated by the ICD system if AT/AF therapies were programmed ‘ON’. However, successful termination of AT episodes was only achieved in 39.6% of all AF episodes (if AT/AF therapies were activated). It has to be taken into consideration that only three patients with AT/AF episodes accepted activation of shock therapy for supraventricular tachyarrhythmias. The efficacy of ATP in combination with a 50 Hz burst in AF is low and was described between 16.8 and 36.2%. In contrast, defibrillation of AF episodes has a success rate of 62.5–92%, depending on the energy used for atrial defibrillation. Therefore, the efficacy of AT/AF termination in this study was within the limits of prior ICD study investigating the Jewel AF ICD and the Jewel GEM III AT ICD.

A first analysis concerning the AF burden performed by the Worldwide Jewel AF investigators showed a significant reduction of the AF burden by treating AT/AF episodes in 52 analysed patients. These patients had a standard indication for ICD implantation and—in contrast to the patients of this study—at least two documented episodes of atrial tachyarrhythmias prior to ICD implantation. The reduction of the AF burden remained significant even if no shocks were programmed for AF therapy. However, the significant reduction was caused by only a few patients with long episodes of AT/AF, which were successfully treated by the ICD system. The majority of patients had no significant reduction of the AF burden. In the following RIF-AF study (126 patients with a clinical indication for ICD implantation, but without a history of AF/AT), no significant change in AT/AF burden was observed if atrial prevention and termination therapies were enabled. This is consistent with the findings of this study. Activation of AT/AF therapies did not result in a reduction of the AF/AT burden in patients with a standard ICD indication, but without a history of AF/AT tachyarrrhythmias. Even in the patients with AF/AT episodes during follow-up, the AF/AT burden was not reduced in case of activated AT/AF therapies. In addition, the overall AF burden was low in this study. Therefore, it is not surprising that the incidence of ventricular tachyarrhythmia could not be reduced in standard ICD patients by implanting a dual-chamber ICD capable of AT/AF treatment. The lower recurrence rate of VT/VF episodes in patients with a history of AF/AT prior to ICD implantation in this study might have been caused by the small subgroup of these patients, resulting in an underpowered subgroup analysis. In concordance with the DAVID trial, standard ICD patients apparently do not benefit from DDD-ICD systems.

**Study limitations**

The study was statistically not powered enough to analyse subgroups of patients, especially the subgroup of patients with paroxysmal AT/AF before ICD implantation. The overall AF burden was too low in this study. The left ventricular ejection fraction was relatively high for an ICD patient population which was probably based on the fact that more than 90% of patients had a secondary prevention ICD indication. Despite attempts to limit bias, there are limitations to the techniques used in this study. Although all episodes were carefully reviewed and classified according to clinical presentation of the patient and information from the device memory, it was not possible to exclude the possibility that some VT/VF episodes were supraventricular tachycardias with rapid ventricular conduction to the ventricles. AT/AF episodes were classified on the basis of rate and regularity of bipolar atrial electrograms. Some episodes classified as AT may have been EP AF. The calculation of the AF/AT burden might be underestimated, as the devices employed in this study had no cardiac compass and AF/AT burden was calculated on the basis of the AF/AT counter of the device. Tachycardias below the detection rate were excluded from this analysis regardless of the tachycardia mechanism, VT or SVT, because they are by definition not collected by the ICD.

**Conclusion**

For patients with standard indication for ICD therapy, a dual-chamber ICD capable of atrial tachyarrhythmia treatment offers no benefit concerning the recurrence rate of ventricular arrhythmias by treating AF/AT episodes. This might be based on the fact that the devices under investigation were not capable of effective atrial tachyarrhythmia treatment. It cannot be excluded that patients with a history of paroxysmal AF or AT and paroxysmal AF/AT episodes during follow-up will benefit from a dual-chamber ICD capable of AT/AF treatment. This study was statistically not powered enough for this specific subgroup of patients. The small group of patients within this study had no benefit by a dual-chamber ICD capable of AT/AF treatment.

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