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RESEARCH ARTICLE

Atrioventricular junction ablation in patients with atrial fibrillation treated with cardiac resynchronization therapy: positive impact on ventricular arrhythmias, implantable cardioverter-defibrillator therapies and hospitalizations

Maurizio Gasparini[1]*, Axel Kloppe[2], Maurizio Lunati[3], Frédéric Anselme[4], Maurizio Landolina[5], Jose Bautista Martinez-Ferrer[6], Alessandro Proclemer[7], Giovanni Morani[8], Mauro Biffi[9], Renato Ricci[10], Roberto Rordorf[11], Lorenza Mangoni[12], Laura Manotta[12], Andrea Grammatico[12], Francisco Leyva[13], and Giuseppe Boriani[14]

[1]Electrophysiology and Pacing Unit, IRCCS Humanitas Research Hospital, Rozzano, Italy; [2]Department of Cardiology, Ruhr-Universität-Bochum, Bochum, Germany; [3]Cardiology Department, Niguarda Hospital, Milan, Italy; [4]Cardiology Department, University Hospital C. Nicolle, Rouen, France; [5]Institute of Cardiology, Maggiore Hospital, Crema, Italy; [6]Department of Cardiology, Hospital de Txagorritxu C/José Achotegui, Vitoria, (Álava), Spain; [7]Department of Cardiology, S. Maria della Misericordia Hospital, Udine, Italy; [8]Cardiology Department, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; [9]Institute of Cardiology, University of Bologna and Azienda Ospedaliera S. Orsola-Malpighi, Bologna, Italy; [10]Department of Cardiology, San Filippo Neri Hospital, Rome, Italy; [11]Department of Cardiology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; [12]Medtronic Regional Clinical Center, Rome, Italy; [13]Aston Medical Research Institute, Aston Medical School, Aston University, Birmingham, UK; and [14]Cardiology Department, Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy

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Aims We sought to determine whether atrioventricular junction ablation (AVJA) in patients with cardiac resynchronization therapy (CRT) implantable cardioverter-defibrillator (ICD) and with permanent atrial fibrillation (AF) has a positive impact on ICD shocks and hospitalizations compared with rate-slowing drugs.

Methods and results This is a pooled analysis of data from 179 international centres participating in two randomized trials and one prospective observational research. The co-primary endpoints were all-cause ICD shocks and all-cause hospitalizations. Out of 3358 CRT-ICD patients (2720 male, 66.6 years), 2694 (80%) were in sinus rhythm (SR) and 664 (20%) had permanent AF—262 (8%) treated with AVJA (AF + AVJA) and 402 (12%) treated with rate-slowing drugs (AF + Drugs). Median follow-up was 18 months. The mean (95% confidence intervals) annual rate of all-cause ICD shocks per 100 patient years was 8.0 (5.3–11.9) in AF + AVJA, 43.6 (37.7–50.4) in AF + Drugs, and 34.4 (32.5–36.5) in SR patients, resulting in incidence rate ratio (IRR) reductions of 0.18 (0.10–0.32) for AF + AVJA vs. AF + Drugs ($P < 0.001$) and 0.48 (0.35–0.66) for AF + AVJA vs. SR ($P < 0.001$).

*Corresponding author. Electrophysiology and Pacing Unit, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano (MI), Italy. Tel: +39 02 82244622, Fax: +39 02 82244693, Email: maurizio.gasparini@humanitas.it

These reductions were driven by significant reductions in both appropriate ICD shocks [IRR 0.23 (0.13–0.40), $P < 0.001$, vs. AF + Drugs] and inappropriate ICD shocks [IRR 0.09 (0.04–0.21), $P < 0.001$, vs. AF + Drugs]. Annual rate of all-cause hospitalizations was significantly lower in AF + AVJA vs. AF + Drugs [IRR 0.57 (0.41–0.79), $P < 0.001$] and SR [IRR 0.85 (073–0.98), $P = 0.027$].

Conclusion In AF patients treated with CRT, AVJA results in a lower incidence and burden of all-cause, appropriate and inappropriate ICD shocks, as well as to fewer all-cause and heart failure hospitalizations.
Clinical Trial Registration: NCT00147290, NCT00617175, NCT01007474.

Keywords Cardiac resynchronization therapy • Atrioventricular junction ablation • Heart failure • Atrial fibrillation

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with mild to severe heart failure (HF), sinus rhythm (SR), a prolonged QRS duration, and impaired left ventricular (LV) systolic function, improving symptoms and LV reverse remodelling, and reducing all-cause mortality.[1–4]

It is well recognized that the development of atrial fibrillation (AF) in HF heralds a poor prognosis.[5–7] There is also evidence to suggest that CRT may not be as effective for patients with AF.[8–12] That may be due to several factors. Firstly, AF precludes atrioventricular optimization of CRT. Secondly, a high intrinsic ventricular response leads to electrical fusion and pseudo-fusion beats, reducing biventricular pacing capture and, consequently, the benefits of CRT. Most randomized, controlled CRT trials have excluded patients with AF. Yet, among the general HF population, AF is common, occurring in 10% to 25% of patients in New York Heart Association (NYHA) class II to III and in as many as 50% of patients in NYHA class IV.[13]

Rate-slowing drugs have been the mainstay of treatment for the control of the ventricular response in patients with AF. Atrioventricular junction ablation (AVJA) has also been used as an alternative to drug therapy.[14] Observational studies have suggested that, in patients with HF and permanent AF undergoing CRT, AVJA is associated with a longer survival compared to treatment with rate-slowing drugs.[8,9,15] In this international, multicentre study, we pooled data from studies on CRT ICD (CRT-D) to evaluate the incidence of ventricular tachycardia/ventricular fibrillation (VT/VF) and ICD therapies, as well as of all-cause and HF hospitalizations in patients with permanent AF, treated with AVJA or rate-slowing drugs, and in patients in SR.

Methods

Study design

We performed a pooled analysis of individual patient data from two prospective, international randomized studies, ADVANCE CRT-D[16] and ADVANCE III,[17] and from the Italian ClinicalService® prospective observational project. Only patients treated with a CRT-D device have been included in this analysis.

ADVANCE CRT-D (ClinicalTrials.gov identifier: NCT00147290) was a prospective, randomized study designed to assess the efficacy of biventricular vs. right ventricular antitachycardia pacing (ATP) in terminating all kinds of ventricular arrhythmias (VT/VF) with 526 patients enrolled from 60 European sites. Study methods and results have already been described.[16]

ADVANCE III (ClinicalTrials.gov identifier: NCT00617175) was a prospective, randomized study designed to assess whether using long detection intervals to detect VT/VF reduces ATP and shock delivery, with 1902 patients enrolled from 94 sites in Europe and Asia. Study methods and results have already been described.[17]

The Italian ClinicalService® project (ClinicalTrials.gov identifier: NCT01007474) is a national cardiovascular data repository and a prospective medical care project aimed at describing and improving the use of implantable cardiac devices in about 150 Italian cardiology centres.

The analysis set includes patients enrolled in 14 countries (Belgium, Denmark, France, Germany, Hungary, Israel, Italy, Portugal, Russia, Saudi Arabia, South Africa, Spain, The Netherland, and UK).

Data collection and analysis was approved by the individual sites' institutional review board or clinical ethics committee and conformed to the Declaration of Helsinki. All patients gave written informed consent for data collection and analysis.

Patient population

Patients were eligible for the pooled database if they were implanted with a CRT-D according to international guidelines [systolic HF in NYHA class III or ambulatory IV, or II in the case of recent HF hospitalization, LV ejection fraction (LVEF) ≤35% and QRS ≥120 ms, despite maximum tolerated pharmacological therapy] and had at least 3-month follow-up and device diagnostic data available.

Our analysis involved 3358 patients who underwent CRT-D implantation from February 2004 to December 2014 in 179 cardiology centres in Europe and Asia (supplementary material online, *Appendix S1*).

Clinical assessment and follow-up

Baseline clinical assessments were undertaken before CRT-D implantation and included evaluation of NYHA class, an electrocardiogram, and transthoracic echocardiography. The following parameters were assessed according to the Simpson's biplane method: LV end-diastolic volume, LV end-systolic volume, and LVEF.[18]

ADVANCE CRT-D and ADVANCE III studies had specified follow-up visits, while in the Italian ClinicalService® clinical follow-ups

Table 1 Baseline characteristics of patient groups

Characteristics	SR ($n = 2694$)	AF + Drugs ($n = 402$)	AF + AVJA ($n = 262$)	*P*-value	Post-hoc comparisons*
Demographics					
Age at first implant (years)	66 ± 10	69 ± 9	69 ± 10	<0.001	1, 3
Male sex	79.8%	87.3%	83.8%	0.001	1
Medical history					
Ischaemic cardiomyopathy	53.3%	44.1%	43.0%	<0.001	1, 3
AMI	49.1%	40.9%	33.2%	<0.001	1, 3
NYHA class III–IV	67.9%	68.4%	76.8%	0.015	
VT/VF	36.5%	32.7%	31.7%	0.15	
LBBB	58.1%	53.0%	40.4%	<0.001	2, 3
QRS (ms)	152 ± 28	142 ± 29	143 ± 32	<0.001	1, 3
Echo parameters					
LVEF (%)	26 ± 6	27 ± 6	28 ± 5	<0.001	2, 3
LVESD (mm)	58 ± 12	55 ± 11	53 ± 8	<0.001	1, 3
LVEDD (mm)	68 ± 10	66 ± 9	63 ± 8	<0.001	2, 3
LVESV (mL)	154 ± 60	141 ± 60	132 ± 61	<0.001	1, 3
LVEDV (mL)	206 ± 72	200 ± 75	181 ± 60	<0.001	3
Pharmacological therapy					
Antiarrhythmic drugs	23.4%	23.3%	19.4%	0.347	
Beta-blockers	70.2%	69.8%	71.2%	0.938	
Diuretics	84.4%	86.0%	87.4%	0.360	
ACEi/ARB	78.5%	72.2%	73.1%	0.005	1, 3
Digitalis	18.9%	30.9%	33.9%	<0.001	1, 3

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; AVJA, atrioventricular junction ablation; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; SR, sinus rhythm; VT/VF, ventricular tachycardia/ventricular fibrillation.
*Post-hoc comparisons are as follows: (1) SR vs. AF + Drugs; (2) AF + AVJA vs. AF + Drugs; (3) SR vs. AF + AVJA.

and device interrogations were performed according to the routine practice of the participating centres.

Rate control strategies

Rate-slowing drugs were given to all AF patients before device implantation and were up-titrated after implantation to reach adequate rate control and to maximize biventricular pacing capture. AVJA was performed within 3 months if adequate biventricular pacing percentage (>95%) did not occur with rate-slowing drugs.[10]

Patient groups

Patients with permanent AF and AVJA performed within 3 months of implant were considered in the AF + AVJA group. Patients with permanent AF and rate control drugs, who were not treated with AVJA, were considered in the AF + Drugs group. Patients without permanent AF were considered in the SR group. In case AVJA was performed during follow-up in SR and AF + Drugs patients, the observation period was censored at the time of ablation. In all patients, follow-up exposure was truncated at 18 months.

Objectives and endpoints

The aim of this analysis was to compare the three groups in terms of: (i) incidence and burden of ICD detections and ICD therapies (ATP and shocks), overall as well as appropriate and inappropriate; and (ii) hospitalizations, taking into account all-cause and HF hospitalizations.

The co-primary endpoints were the annual rates of all-cause ICD shocks and all-cause hospitalizations. Secondary endpoints were: (i) annual rate of appropriate ICD shocks, (ii) annual rate of inappropriate ICD shocks, (iii) incidence of all-cause, appropriate, and inappropriate ICD shocks, and (iv) HF hospitalizations.

Appropriateness of all sustained VT/VF, and monitored VT detected by implanted devices was analysed by two members of a blinded episode review committee who reviewed episodes plots and electrograms. In the case of disagreement between the two reviewers, the episode was submitted to a third independent reviewer.

Device therapy

Transvenous CRT-D implantation was undertaken using standard transvenous techniques under local anaesthesia. A lateral or posterolateral LV site was considered optimal for LV lead by most implanters. In patients with SR, the CRT device was programmed in atrial–synchronous sequential pacing. For patients with AF, rate

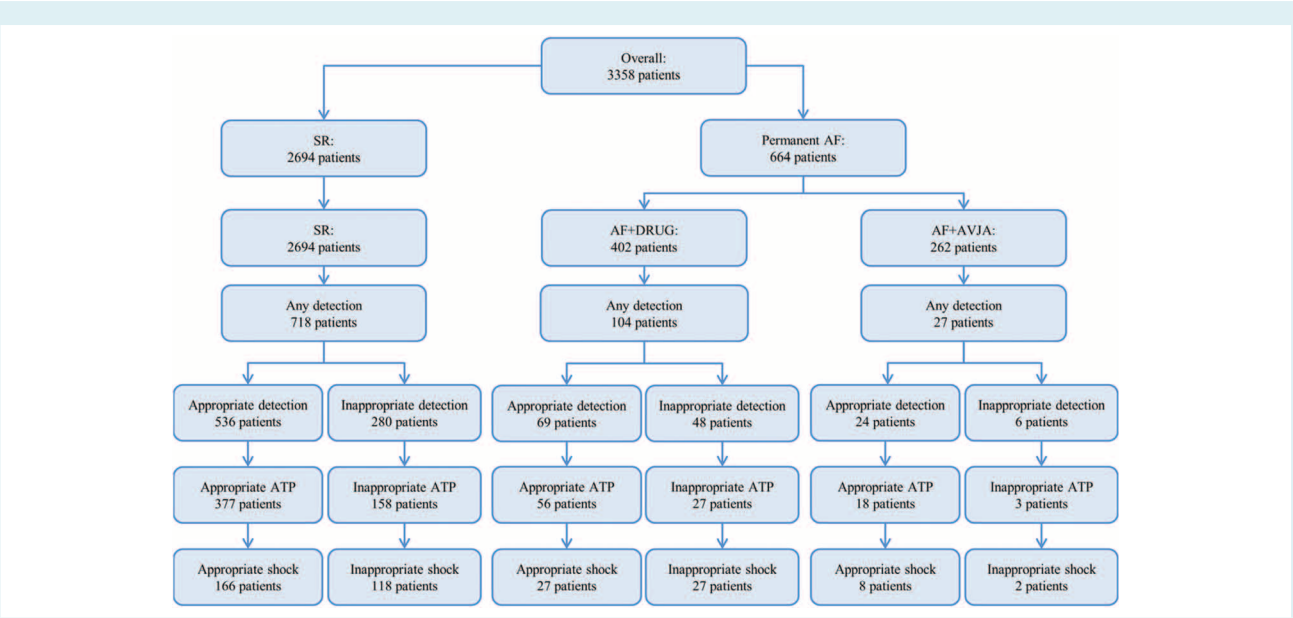

Figure 1 Ventricular tachyarrhythmia detections and implantable cardioverter-defibrillator therapies: number of patients in each research group and number of patients with implantable cardioverter-defibrillator detection, antitachycardia pacing (ATP) and shocks, overall and for appropriate and inappropriate episodes, respectively. AF, atrial fibrillation; AVJA, atrioventricular junction ablation; SR, sinus rhythm.

response was activated, the minimum heart rate was set at ≥70 b.p.m. and the maximum rate was set at 70% of the maximum heart rate. Programming of some device features was according to the different study protocols[16,17] or left to the discretion of the treating physician. Importantly, there were no differences in pacing features and tachycardia detection programming among the analysed groups.

Statistical analysis

Continuous variables were expressed as means and standard deviations, or median and interquartile range (IQR), as appropriate. Categorical variables were expressed as counts and percentages. Baseline characteristics were compared between groups by means of chi-square test or Kruskal–Wallis test, as appropriate. Analysis of all-cause ICD shocks, as well as appropriate detections and therapies, followed the same approach and the same blind review that was used in the ADVANCE III trial.[17] Rates were computed for 100 person years and were compared by means of the Poisson model using the scale deviation parameter to adjust for over-dispersion. Incidence rate ratios (IRRs) with their 95% confidence intervals (CIs) were computed to measure episodes and hospitalization reductions in the AF + AVJA group. IRRs were also adjusted to account for the effect of potential confounders in the comparison between AF + AVJA and AF + Drugs. A sub-group of 336 patients (209 SR patients, 86 AF + Drugs patients, and 41 AF + AVJA patients) received a new generation CRT-D device with an out of the box programming which, once implemented by implanters, resulted in a by-default strictly homogeneous programming among study groups and allowed to perform a sensitivity analysis to confirm results found in the whole patient cohort. Freedom from ICD detection or therapy and from hospitalization were studied by means of a Cox model, and Kaplan–Meier curves were reported. Univariate hazard ratios (HRs) with their 95% CIs were reported. An alpha-level of 0.05 was considered for each test. All statistical analyses were performed using SAS 9.4 version software (SAS Institute Inc., Cary, NC, USA).

Results

A total of 3358 patients with CRT-D were included in the analysis; patients were classified into three groups: 2694 (80%) SR patients, 402 AF + drugs patients (12%), and 262 AF + AVJA patients (8%). Patient characteristics are shown in *Table 1*. Patients with AF were older, less likely to have ischaemic cardiomyopathy or previous acute myocardial infarction or a wide QRS, and had smaller LV dimensions. Comparing patients with AF + AVJA vs. AF + drugs, the former had slightly higher LVEF and were less likely to have left bundle branch block (LBBB).

In a median (IQR) follow-up of 18 (12–18) months, ICD episodes and therapies were collected, reviewed by the blinded episode review committee and defined as appropriate or inappropriate as described in *Figure 1*.

Co-primary endpoints: all-cause implantable cardioverter-defibrillator shocks and hospitalizations

Annual rate of all-cause ICD shocks was 34.4 (32.5–36.5) in the SR group, 43.6 per 100 patient years in the AF + Drugs group, and 8.0 per 100 patient years in the AF + AVJA group, associated with a significant 82% reduction (IRR 0.18, 95% CI 010–0.32; $P < 0.001$) comparing AF + AVJA vs. AF + Drugs (*Figure 2A*), and a significant 52% reduction (IRR 0.48, 95% CI 0.35–0.66; $P < 0.001$) comparing AF + AVJA vs. SR (*Figure 2B*).

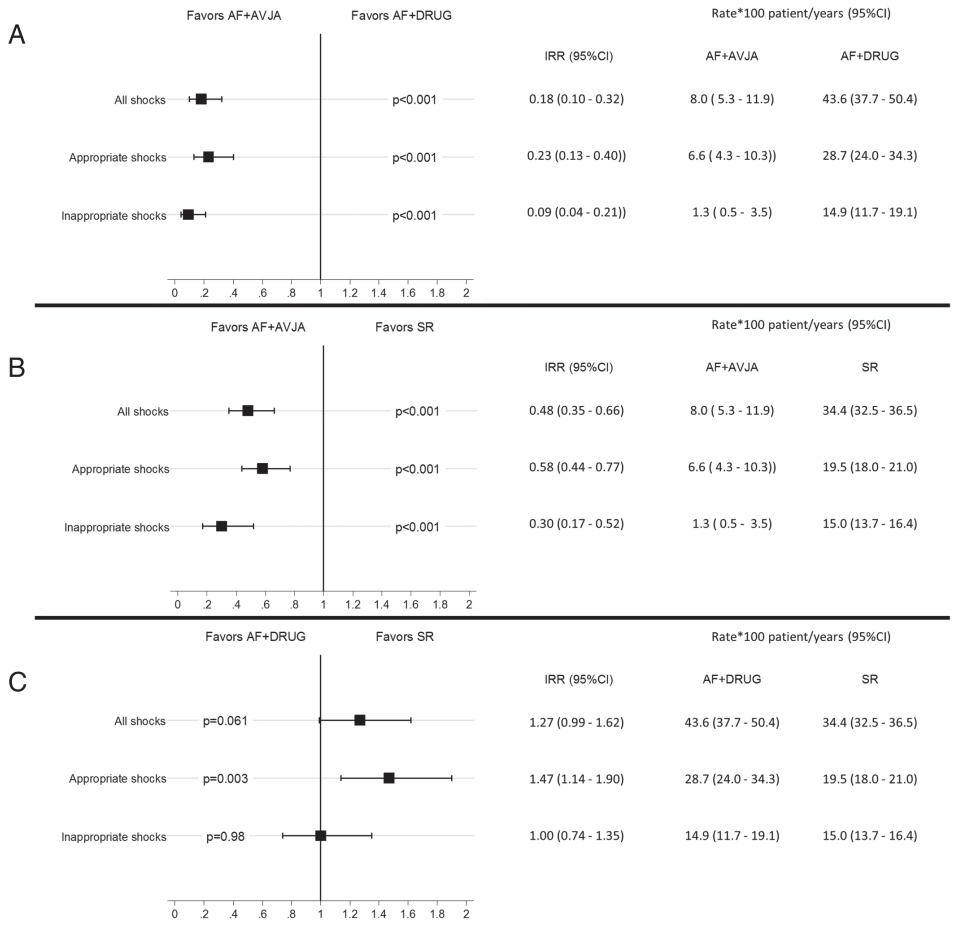

Figure 2 Incidence rate ratios (IRR) and annual rates of all-cause, appropriate and inappropriate implantable cardioverter-defibrillator shocks in AF + AVJA vs. AF + Drugs patients (*A*), AF + AVJA vs. SR patients (*B*), and AF + Drugs vs. SR patients (*C*). AF, atrial fibrillation; AVJA, atrioventricular junction ablation; CI, confidence interval; SR, sinus rhythm.

A significant IRR reduction (IRR 0.28, 95% CI 0.16–0.51; $P < 0.001$) comparing AF + AVJA vs. AF + Drugs was confirmed after correction for use of a new generation CRT-D or LVEF and LBBB, which were the patients' baseline characteristics that resulted as different between AF + AVJA and AF + Drugs groups. Similarly, a significant IRR reduction (IRR 0.54, 95% CI 0.39–0.76, $P < 0.001$) comparing AF + AVJA vs. SR was confirmed after correction for use of a new generation CRT-D and for the baseline characteristics that were different between AF + AVJA and SR groups. Together with all-cause ICD shocks, also all-cause ICD detections and ATP showed a significantly lower annual rate in AF + AVJA vs. both AF + Drugs and SR ($P < 0.001$) (supplementary material online, *Tables S1–S3*).

AF + Drugs patients showed a trend toward higher annual rate of all-cause ICD shocks as compared to SR patients (*Figure 2C*).

During follow-up, 684 patients were hospitalized for any reason [557 (20.7%) in the SR group, 88 (33.1%) in the AF + Drugs group, and 39 (18.1%) in the AF + AVJA group]. Annual rates of all-cause hospitalizations for AF + AVJA patients were significantly lower than in AF + Drugs or SR groups (*Table 2*). In particular, a significant IRR reduction (IRR 0.57, 95% CI 0.41–0.79; $P < 0.001$) was found comparing AF + AVJA vs. AF + Drugs, and even the comparison between AF + AVJA and SR was favourable (IRR 0.85, 95% CI 073–0.98; $P = 0.027$).

AF + AVJA patients showed significantly higher freedom from all-cause ICD shocks compared with AF + Drugs or SR patients (*Figure 3A*).

Appropriate detections and therapies

The annual rate of appropriate ICD shocks was 19.5 in the SR group, 28.7 per 100 patient years in the AF + Drugs group, and 6.6 per 100 patient years in the AF + AVJA group, resulting in a significant 77% reduction (IRR 0.23, 95% CI 0.13–0.40; $P < 0.001$) comparing AF + AVJA vs. AF + Drugs (*Figure 2A*), and a significant 42% reduction (IRR 0.58, 95% CI 0.44–0.77; $P < 0.001$) comparing AF + AVJA vs. SR (*Figure 2B*).

A significant IRR reduction comparing AF + AVJA vs. AF + Drugs was confirmed after correction for use of a new generation CRT-D or LVEF and LBBB (IRR 0.46, 95% CI 0.27–0.79; $P = 0.005$).

Table 2 All-cause hospitalizations

Rhythm group	Patients (*n*)	All-cause hospitalizations (*n*)	Annual rate * 100 patient years (95% CI)	IRR (95% CI)	*P*-value
SR	557 (20.7%)	808	24.4 (24.1–24.6)		
AF + Drugs	88 (33.1%)	130	30.8 (29.9–31.6)	1.26 (1.04–1.54) vs. SR	0.020
AF + AVJA	39 (18.1%)	53	17.6 (17.0–18.1)	0.85 (073–0.98) vs. SR 0.57 (0.41–0.79) vs. AF + Drugs	0.027 <0.001

AF, atrial fibrillation; AVJA, atrioventricular junction ablation; CI, confidence interval; IRR, incidence rate ratio; SR, sinus rhythm.

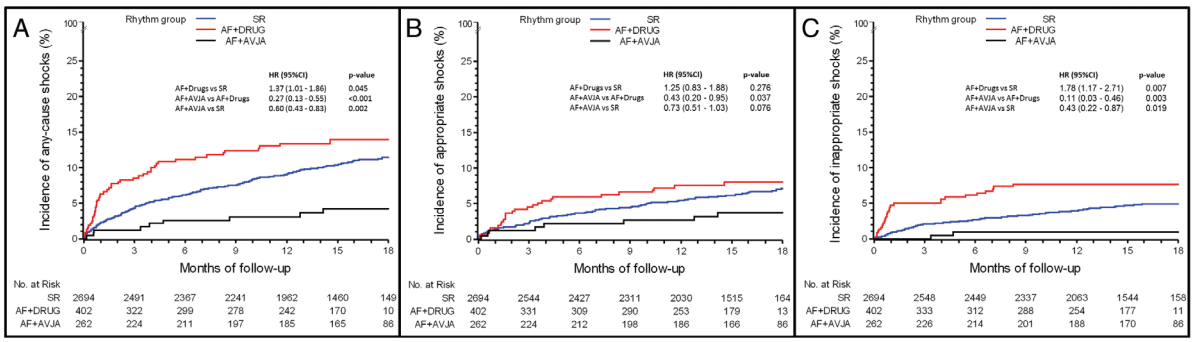

Figure 3 Incidence of implantable cardioverter-defibrillator (ICD) shocks: time to first all-cause ICD shock (*A*), first appropriate ICD shock (*B*), and first inappropriate ICD shock (*C*). AF, atrial fibrillation; AVJA, atrioventricular junction ablation; CI, confidence interval; HR, hazard ratio; SR, sinus rhythm.

Similarly, a significant IRR reduction (IRR 0.67, 95% CI 0.49–0.91; $P = 0.01$) comparing AF + AVJA vs. SR was confirmed after correction for use of a new generation CRT-D and for the baseline characteristics that were different between AF + AVJA and SR groups.

AF + Drugs patients showed a significantly higher annual rate of appropriate ICD shocks as compared to SR patients (*Figure 2C*).

Patients with AF + AVJA showed a lower incidence of appropriate ICD shocks compared with both AF + Drugs and SR patients (*Figure 3B*). Together with appropriate ICD shocks, also appropriate ICD detections and ATP showed a significantly lower annual rate in AF + AVJA vs. both AF + Drugs and SR ($P \leq 0.003$) (supplementary material online, *Tables S4–S6*).

Inappropriate detections and therapies

The annual rate of inappropriate ICD shocks was 15.0 in the SR group, 14.9 per 100 patient years in the AF + Drugs group, and 1.3 per 100 patient years in the AF + AVJA group, resulting in a significant 91% reduction (IRR 0.09, 95% CI 0.04–0.21; $P < 0.001$) between AF + AVJA and AF + Drugs (*Figure 2A*) and a significant 70% reduction (IRR 0.30, 95% CI 0.17–0.52; $P < 0.001$) between AF + AVJA and SR (*Figure 2B*).

A significant IRR reduction was confirmed when comparing AF + AVJA vs. AF + Drugs after correction for use of a new generation CRT-D or LVEF and LBBB (IRR 0.09, 95% CI 0.03–0.24; $P < 0.001$). Similarly, a significant IRR reduction (IRR 0.31, 95% CI 0.16–0.59; $P < 0.001$) comparing AF + AVJA vs. SR was confirmed after correction for use of a new generation CRT-D and for the baseline characteristics that were different between AF + AVJA and SR groups. Together with inappropriate ICD shocks, also inappropriate ICD detections and ATP showed a significantly lower annual rate in AF + AVJA vs. both AF + Drugs and SR ($P < 0.001$) (supplementary material online, *Tables S7–S9*).

The annual rate of inappropriate ICD shocks did not differ between AF + Drugs and SR patients (*Figure 2C*). Patients with AF + AVJA showed a lower incidence of inappropriate ICD shocks compared with both AF + Drugs ($P = 0.003$) and SR ($P = 0.019$) patients (*Figure 3C*); in particular, at 12 months the incidence of inappropriate ICD shocks was 3.9% (3.2%–4.8%) in SR patients, 7.7% (5.3%–11.0%) in AF + Drugs patients, and 0.9% (0.2%–3.6%) in AF + AVJA patients.

Most inappropriate detections and therapies were due to AF, in particular AF was the cause for inappropriate detections in 1104/1405 (78.6%) episodes and in 270/334 (80.8%) patients with inappropriate detections; moreover, 300/359 (83.6%) episodes with inappropriate ICD shocks were due to AF. However, AF + AVJA patients were almost free from inappropriate VT/VF detections induced by AF; only 6/262 (2.3%) patients had

Table 3 Heart failure hospitalizations

Rhythm group	Patients (*n*)	HF hospitalizations (*n*)	Annual rate * 100 patient years (95% CI)	IRR (95% CI)	*P*-value
SR	191 (7.1%)	265	8.0 (7.9–8.1)		
AF + Drugs	30 (7.5%)	40	9.5 (9.2–9.7)	1.18 (0.92–1.52) vs. SR	0.183
AF + AVJA	13 (5.0%)	15	5.0 (4.8–5.1)	0.79 (0.65–0.95) vs. SR 0.52 (0.35–0.78) vs. AF + Drugs	0.016 0.002

AF, atrial fibrillation; AVJA, atrioventricular junction ablation; CI, confidence interval; HF, heart failure; IRR, incidence rate ratio; SR, sinus rhythm.

one AF-related inappropriate detection and only 2 (0.8%) patients suffered one single shock each in one episode. The annual rate of AF-related ICD shocks was 0.7 per 100 patient years in the AF + AVJA group, 11.6 per 100 patient years in the AF + Drugs group, and 12.6 per 100 patient years in the SR group, resulting in a significant 94% reduction (IRR 0.06, 95% CI 0.02–0.166; $P < 0.001$) comparing AF + AVJA vs. AF + Drugs, and a significant 77% reduction (IRR 0.23, 95% CI 0.11–0.48; $P < 0.001$) comparing AF + AVJA vs. SR. Together with AF-related inappropriate ICD shocks, also AF-related inappropriate ICD detections and ATP showed a significantly lower annual rate in AF + AVJA vs. both AF + Drugs and SR ($P < 0.001$) (supplementary material online, *Tables S10–S12*).

Heart failure hospitalizations

During follow-up, 234 patients were hospitalized for HF [191 (7.1%) in the SR group, 30 (7.5%) in the AF + Drugs group, and 13 (5.0%) in the AF + AVJA group]. Annual rates of HF hospitalization for 100 patient years were 8.0 (7.9–8.1) in the SR group, 9.5 (9.2–9.7) in the AF + Drugs group, and 5.0 (4.8–5.1) in the AF + AVJA group, resulting in a significant 48% reduction (IRR 0.52, 95% CI 0.35–0.78; $P = 0.002$) comparing AF + AVJA vs. AF + Drugs, and a 21% significant reduction (IRR 0.79, 95% CI 0.65–0.95; $P = 0.016$) comparing AF + AVJA vs. SR (*Table 3*).

Biventricular pacing

The median percentage of biventricular pacing was 98% (IQR 97%–98%) in the SR group, 93% (IQR 83%–98%) in the AF + Drugs group, and 97% (IQR 93%–98%) in the AF + AVJA group ($P < 0.001$ at Wilcoxon rank-sum test comparing AF + AVJA vs. AF + Drugs and SR vs. AF + Drugs).

Discussion

Main results

Our findings show that in AF patients treated with CRT, AVJA results in a lower incidence and burden of all-cause ICD shocks, as well as fewer all-cause and HF hospitalizations compared to a rate-control drug strategy. The positive effect was driven by reductions in both appropriate and inappropriate ICD shocks. Importantly, these reductions were also evident when comparing CRT-D patients with permanent AF patients treated with AVJA vs. CRT-D patients in SR. Noteworthy, these results were also confirmed after correction for differences in baseline characteristics.

The annual rates of appropriate or inappropriate detections and ATP were significantly reduced in patients treated with AVJA compared with AF patients treated with rate control agents or in SR. Moreover, the ratio between inappropriate and appropriate therapies, that is an important performance indicator of ICD therapy, was notably lower in the AF + AVJA group than in the other groups.

CRT patients treated with AVJA have lower all-cause and HF hospitalizations and this finding, previously not analysed in this subset of patients, widens the benefits shown by previous studies and meta-analyses[9,10,15,19,20] that highlighted reduced mortality in patients treated with AVJA as opposed to rate control agents. Noteworthy, ICD therapies, particularly shocks, have a negative impact on quality of life and prognosis.[21,22] The lower rates of all-cause and HF hospitalizations can have important implications in the costs of post-CRT implant HF patients and allow to consider that the positive impact of CRT on hospitalizations demonstrated for patients with SR[3,4] can be achieved also in patients with permanent AF, if AVJA is performed as an alternative to rate control drugs.

These findings are of particular relevance and have an important value for improving patient management, given that no randomized controlled trials have compared AVJA and rate control drug strategies in CRT-D recipients, although the prevalence of permanent AF in such CRT population approaches 25%.[23,24] So far, only some observational studies[9,10,15] and two meta-analyses[19,20] have evaluated these two rate control strategies and have suggested that for CRT patients with AF, AVJA is associated with better clinical outcomes and a > 50% reduction in all-cause mortality compared with rate-slowing drugs. It is on this basis that the 2012 European Society of Cardiology (ESC) guidelines[25] proposed atrioventricular node ablation in CRT patients unable to tolerate or with an inadequate response to rate control agents and that current ESC guidelines[26] now consider HF patients with permanent AF

as candidates for CRT (class IIa, level of evidence B), provided a strategy to ensure biventricular capture is in place.

Our data on the incidence and burden of arrhythmic events and all-cause and HF hospitalizations provide further support to the use of AVJA in AF patients treated with CRT and add new insight on the physiologic mechanisms that could explain AVJA positive impact on mortality. The observation that AVJA reduces appropriate ICD detections and therapies, that is an important finding, may be explained by the fact that AVJA prevents short–long–short sequences that are a well-recognized triggers of VT/VF, specifically in patients with low ejection fraction during rapid AF.[27] Moreover, AVJA may prevent the negative impact of rapidly conducted AF on CRT, through reduction of biventricular pacing percentage. In a cohort of 36 935 CRT patients followed up in a remote-monitoring network, Hayes *et al.*[28] showed that a biventricular pacing uptake higher than 98% was required to achieve a reduction in mortality. In this analysis, patients with permanent AF and treated with AVJA were almost completely free from inappropriate VT/VF detections induced by AF. Speculatively, the few cases in which inappropriate ICD shocks occurred were probably due to incomplete AVJA or modulation. The incidence of inappropriate ICD shocks at 1 year after implant was 0.9% in AF + AVJA patients, 7.7% in AF + Drugs patients, and 3.9% in SR patients, the latter being comparable with incidences found by recent trials, such as 2.6% reported in the long detection arm of ADVANCE III[17] and 3% reported in the delayed therapy arm of MADIT-RIT.[21] Lower incidences of inappropriate ICD shocks, in the range of 0.9% to 1.5%, have recently been reported by studies evaluating novel discrimination algorithms.[29,30] However, it is worthwhile mentioning that not all ICD used in clinical practice feature those specific shock suppression algorithms and that no data have been reported on the performance of those algorithms in CRT-D patients with permanent AF.

Our observation that patients classified as being in SR had a higher incidence of both AF-related inappropriate ICD detections and therapies and appropriate ICD detections and therapies, compared with AF + AVJA patients, may be a reflection of undetected paroxysmal or new-onset AF in the SR group.

Clinical implications

Despite recommendations by the ESC and the American Heart Association[25,26,31] to maximize biventricular pacing in CRT patients with AF using AVJA, this technique is still underused, likely because it leads to pacemaker dependence. Several observational studies[9,10,15] and two meta-analyses[19,20] have shown that, in CRT patients with AF, AVJA is associated with better LV reverse remodelling and clinical outcomes compared to rate control drugs. Our data also show that AVJA in CRT patients with AF is associated with a clinically significant reduction in ICD therapies as well as all-cause and HF hospitalizations, and this can have important economic implications. The implications for daily practice are that the positive impact of CRT on hospitalizations in patients with SR[3,4] can be achieved also in patients with permanent AF, if AVJA is performed instead of using rate control drugs.[15]

Since AF represents an important co-morbidity of HF patients and co-morbidity burden has recently been associated with worst prognosis in patients with ICD,[32] our results reinforce the proposal[25,31] of AVJA in patients with HF, permanent AF and candidates for CRT who are not responding to rate control agents.

Study limitations

We recognize that our analysis has some limitations. Assigning AVJA or rate control drugs was not randomized, rather left to the practice of cardiologists involved in the three clinical projects from which data were gathered. As a consequence, patient distribution was unbalanced and unequally distributed: 80% of patients were in SR, 12% had AF + drugs and 8% had AF + AVJA. Confounding factors include differences in patient populations and follow-up timing between the three studies. We tried to optimize scientific methodology by pre-specifying analysis objectives before data set opening and by correcting arrhythmic event risk for most important patient characteristics, in particular for those which differed among analysed groups. Moreover, a homogeneous review of ICD detections and therapies was performed in all patient groups by a blinded episode review committee.[17] We acknowledge that a detailed review of episode recordings could have disclosed to reviewers which group the subject belonged to; we believe that blinding was anyhow assured in the majority of cases, and therefore findings were not influenced. AVJA was performed if biventricular pacing percentage was below 95%. However, it is known that the percentages of biventricular pacing given by the device may be false positive due to fusion or pseudo-fusion due to conducted AF. The cut-off of 95% biventricular pacing which triggered cardiologists' decision about AVJA was arbitrarily defined on the basis of literature data that identified in that value a threshold for CRT clinical impact; we recognize that in each patient fusion or pseudo-fusion events may have slightly changed the patient specific effective pacing percentage.

We provide no data on mortality or device infections, the latter being a potentially serious adverse event specifically in patients with atrioventricular node ablation.

Conclusions

In CRT-D patients with permanent AF, AVJA is associated with a lower rate and incidence of ICD shocks as well as ATP and detections, both appropriate and inappropriate, compared with a rate control drug strategy. Moreover, AVJA is associated with a lower incidence of all-cause and HF hospitalizations, a previously unreported finding with potentially favourable economic implications. Further randomized studies on the role of AVJA in patients with AF undergoing CRT are warranted.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Research Committees and participating centres.

Table S1. All-cause detections.

Table S2. All-cause ATP.
Table S3. All-cause shocks.
Table S4. Appropriate detections.
Table S5. Appropriate ATP.
Table S6. Appropriate shocks.
Table S7. Inappropriate detections.
Table S8. Inappropriate ATP.
Table S9. Inappropriate shocks.
Table S10. AF-related inappropriate detections.
Table S11. AF-related inappropriate ATP.
Table S12. AF-related inappropriate shocks.

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