Incidence of ventricular arrhythmias and ICD therapies in patients with heart failure, atrial fibrillation and cardiac resynchronization therapy. A pooled analysis of prospective studies.

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ABSTRACT

Background. Several studies demonstrated that cardiac resynchronization therapy (CRT) is effective in treating heart failure (HF) patients who are in sinus rhythm (SR) and that atrioventricular junction ablation (AVJA) improves prognosis in CRT patients with atrial fibrillation (AF). We aimed to determine whether AVJA reduces incidence and burden of ventricular tachyarrhythmias (VT/VF) and of all-cause ICD therapies compared with treatment with rate-slowing drugs, in CRT patients with permanent AF.

Methods. Pooled analysis of patient data from the Advance CRT-D and Advance III randomized trials, and from the Italian ClinicalService® prospective observational project. Primary endpoint was the annual rate of all-cause ICD shocks.

Results. A total of 3358 patients (2720 male, mean age 66.6 years) with CRT-ICD were included by 179 International centers; 2694 (80%) SR patients, 262 permanent AF patients treated with AVJA (AF+AVJA, 8%) and 402 AF patients treated with rate-slowing drugs (AF+Drugs, 12%). Median follow-up was 18 months. The rate of all-cause shocks (95% confidence interval) 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, with an incidence rate reduction (IRR) of 0.18 (0.10-0.32) comparing AF+AVJA with AF+Drugs ($p<0.001$) and IRR=0.48 (0.35-0.66) comparing AF+AVJA with SR ($p<0.001$). Also the rates of appropriate and inappropriate shocks, when considered separately, were reduced in patients with AF+AVJA compared with AF+Drugs and SR patients.

Conclusions. CRT-D patients with permanent AF have lower incidence and burden of ICD shocks both appropriate and inappropriate, when treated with AVJA compared with rate control agents.

Keywords: *cardiac resynchronization therapy, atrio-ventricular 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. (1-4) In the CARE-HF (Cardiac Resynchronization in Heart Failure) study (4), CRT was associated with 40% relative reduction in all-cause mortality. This and other studies have shown that CRT also improves symptoms, exercise capacity, and quality of life, and induces LV reverse remodeling. (5-6)

It is well recognized that the development of atrial fibrillation (AF) in HF heralds a poor prognosis. (7-9) There is also evidence to suggest that CRT may not be as effective for patients with AF. (10-15). 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, CRT benefits. 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. (16)

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 for controlling the ventricular response in patients with permanent AF. (17)

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. (10-11, 18). In this large international, multicenter research we pooled data from studies on CRT ICD (CRT-D) to evaluate VT/VF incidence and ICD therapies in patients with permanent AF, treated by AVJA or rate-slowing drugs, and in patients in SR.

Methods

Design

We performed a pooled analysis of individual patient data from two prospective, international randomized studies, Advance CRT-D (19) and Advance III (20), 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 versus 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 been already described. (19)

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 been already described. (20)

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 centers.

The analysis set includes patients enrolled in 14 countries, in particular 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 a

recent HF hospitalization); LVEF≤35% and QRS≥120 ms, despite maximum tolerated pharmacologic therapy and had at least 3 months of follow-up and device diagnostic data available. Our analysis involved 3358 patients who underwent CRT-D implantation in the period from February 2004 to December 2014 in 179 cardiological centers in Europe and Asia (see Appendix).

Clinical assessment and follow-up

Baseline clinical assessments were undertaken before CRT-D implantation and included evaluation of NYHA class, an electrocardiogram, and a transthoracic echocardiogram. The following parameters were assessed according to the Simpson's biplane method: LV end-diastolic volume, LV end-systolic volume (LVESV), and LVEF. (21)

Advance CRT-D and Advance III studies had specified follow-up visits, while in the Italian ClinicalService® clinical follow-ups and device interrogations were performed according to the routine practice of the participating centers.

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 (22), and to maximize the biventricular pacing capture. The AVJA was performed within 3 months if adequate biventricular pacing percentage did not occur with rate-slowing drugs. (12)

Patient groups

Patients with permanent AF and AVJA performed within 3 months from implant were considered in the AF+AVJA group. Patients with permanent AF and rate control drugs, who were not treated by 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 the ablation. In all patients, the follow-up exposure was trunked at 18 months.

Objectives and endpoints

Aim of this analysis was to compare the 3 groups in term of incidence and burden of ICD detections and ICD therapies (ATP and shocks), overall as well as appropriate and inappropriate. The primary

endpoint was the annual rate of any cause ICD shocks. Secondary endpoints were 1) annual rate of appropriate shocks, 2) annual rate of inappropriate shocks, 3) incidence of all-cause, appropriate, and inappropriate shocks. We also evaluated all-cause and heart failure hospitalizations.

Appropriateness of all sustained ventricular tachycardias, ventricular fibrillations, and monitored ventricular tachycardias detected by implanted devices was analyzed by 2 members of a blind episode review committee (ERC) who reviewed episodes plots and electrograms. In the case of disagreement between the 2 reviewers, the episode was submitted to a third independent reviewer.

Device therapy

Transvenous CRT-D implantation was undertaken using standard transvenous techniques under local anesthesia. 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. Atrioventricular optimization was undertaken within 24 hours of device implantation and at 6 months, using Doppler echocardiography and the iterative method (20). For patients with AF, the minimum heart rate was set at ≥70 beats/min and the maximum rate was set at 70% of the theoretical maximum heart rate.

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 the chi-square test or the Kruskal-Wallis test as appropriate. Analysis of primary endpoints (all-cause ICD shocks) as well as analysis of appropriate detections and therapies, followed the same approach and the same blind review that was used in the Advance III trial. (20) 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 (95%CI) were computed to measure episodes and hospitalizations reduction 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. 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%CI were reported. An alpha-level of 0.05 was considered for each test. All statistical analyses were performed by using SAS 9.4 version software (SAS Institute Inc., Cary, NC, USA).

Results

A total of 3358 patients with CRT ICD were included in the analysis; patients were classified into 3 groups, 2694 (80%) SR patients, 402 AF+drugs patients (12%) and 262 AF+AVJA patients (8%).Patient characteristics are shown in Table I; patients with AF were older, less likely to have an ischemic cardiomyopathy or previous acute myocardial infarction (AMI) or a large QRS and had smaller LV dimensions. Comparing patients with AF+AVJA and patients with AF+drugs, the former had slightly higher LVEF and were less likely to have left bundle branch block.

In a median (IQR) follow up of 18 (12-18) months, ICD episodes and therapies were collected, reviewed by the blind ERC and defined as appropriate or inappropriate as described in figure 1.

Primary endpoint – all-cause ICD shocks

Annual rate of all-cause ICD shocks was 8.0 per 100 patient years in the AF+AVJA, 43.6 per 100 patient years in the AF+Drugs group and 34.4 (32.5 - 36.5) in SR group leading to a significant 82% reduction (IRR (95%CI)=0.18 (010-0.32), p<0.001) comparing AF+AVJA vs. AF+Drugs as shown in figure 2 section A and a significant 52% reduction (IRR (95%CI)=0.48 (0.35 - 0.66), p<0-001) comparing AF+AVJA vs. SR as shown in figure 2 section B.

A significant IRR reduction (IRR (95%CI)=0.31 (0.17-0.56), p<0.001) comparing AF+AVJA vs. AF+Drugs was confirmed after correction for LVEF and LBBB which were patients' baseline characteristics which resulted as different between AF+AVJA an AF+Drugs groups.

Together with all-cause shocks, also all-cause ICD detections and ATP showed a significantly (p<0.001) lower annual rate in AF+AVJA group compared with both AF+Drugs group and SR group (tables 0:1-0:3 in appendix supplementary data).

AF+Drugs patients showed a trend toward higher annual rate of all-cause ICD shocks vs. SR patients, as shown in figure 2 section C.

Secondary endpoints

AF+AVJA patients showed significantly higher freedom from all-cause ICD shocks compared with AF+Drugs patients or SR patients, as shown in figure 3A.

Appropriate detections and therapies

The annual rate of appropriate ICD shocks was 6.6 per 100 patient years in the AF+AVJA, 28.7 per 100 patient years in the AF+Drugs group and 19.5 (18.0 - 21.0) in the SR group, leading to a significant 77% reduction (IRR (95%CI)=0.23 (0.13-0.40), p<0.001) comparing AF+AVJA and AF+Drugs as shown in figure 2 section A, and a significant 42% reduction (IRR (95%CI)=0.58 (0.44 - 0.77), p<0.001) comparing AF+AVJA and SR as shown in figure 2 section B.

A significant IRR reduction comparing AF+AVJA vs. AF+Drugs was confirmed after correction for LVEF and LBBB (IRR (95%CI)=0.50 (0.29-0.87), p=0.015).

AF+Drugs patients showed significantly higher annual rate of appropriate ICD shocks vs. SR patients, as shown in figure 2 section C.

Patients with AF+AVJA showed lower incidence (figure 3B) of appropriate shocks both compared with AF+Drugs and SR patients.

Together with appropriate shocks, also appropriate ICD detections and ATP showed a significantly ($p \leq 0.003$) lower annual rate in AF+AVJA group compared with both AF+Drugs group and SR group (tables 0:4-0:6 in appendix supplementary data).

Inappropriate detections and therapies

The annual rate of inappropriate ICD shocks was 1.3 per 100 patient years in the AF+AVJA, 14.9 per 100 patient years in the AF+Drugs group and 15.0 (13.7-16.4) in the SR group leading to a significant 91% reduction (IRR (95%CI)=0.09 (0.04-0.21), p<0.001) between AF+AVJA and AF+Drugs as shown in figure 2 section A and a significant 70% reduction (IRR (95%CI)=0.30 (0.17 - 0.52), p<0.001) between AF+AVJA and SR as shown in figure 2 section B.

A significant IRR reduction was confirmed when comparing AF+AVJA vs. AF+Drugs after correction for LVEF and LBBB (IRR (95%CI)=0.09 (0.03-0.26), p<0.001).

Together with inappropriate shocks, also inappropriate ICD detections and ATP showed a significantly lower ($p<0.001$) annual rate in AF+AVJA group compared with both AF+Drugs group and SR group (tables 0:7:0.9 in appendix supplementary data).

Annual rate of inappropriate ICD shocks was not different between AF+Drugs patients and SR patients, as shown in figure 2 section C.

Patients with AF+AVJA showed lower incidence (figure 3C) of inappropriate shocks both compared with AF+Drugs ($p=0.003$) and SR ($p=0.019$) 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%) of patients with inappropriate detections; moreover 300/359 (83.6%) episodes with inappropriate ICD shocks were due to AF. However patients in the AF+ AVJA group were almost free from inappropriate VT/VF detections induced by AF; only 6/262 (2.3%) patients had one AF-related inappropriate detection and only 2 (0.8%) patients suffered 1 single shock each in 1 episode. Annual rate of AF-related ICD shocks was 0.7 per 100 patient years in the AF+AVJA, 11.6 per 100 patient years in the AF+Drugs group and 12.6 per 100 patient years in the SR group leading to a significant 94% reduction (IRR (95%CI)=0.06 (0.02-0.166), $p<0.001$) comparing AF+AVJA vs. AF+Drugs and a significant 77% reduction (IRR (95%CI)=0.23 (0.11-0.48), $p<0.001$) comparing AF+AVJA vs. SR. Together with AF-related inappropriate shocks, also AF-related inappropriate ICD detections and ATP showed a significantly ($p<0.001$) lower annual rate in AF+AVJA group compared with both AF+Drugs group and SR group (tables 0:10-0:12 in appendix supplementary data).

Overall and heart failure hospitalizations

During follow-up 684 patients were hospitalized for any reason, in particular 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 rate of all-cause hospitalizations for the AF+AVJA patients were significantly lower than in AF+Drugs or SR groups, as shown in table II.

During follow-up 234 patients were hospitalized for heart failure, in particular 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 rate of heart failure hospitalization for 100 patient years were 8.0 (7.9-8.1) in SR patients, 9.5 (9.2-9.7) in the AF+Drugs group and 5.0 (4.8-5.1) in the AF+AVJA group leading to a significant 48% reduction (IRR (95%CI)=0.52 (0.35-0.78) p=0.002) comparing AF+AVJA and AF+Drugs patients and a 21% significant reduction (IRR (95%CI)=0.79 (0.65-0.95) p=0.016) comparing AF+AVJA and SR patients, as shown in table III.

Discussion

Main results

By comparing CRT-D patients with permanent AF we found that the strategy of AVJA was associated with lower burden and incidence of all-cause ICD shocks, and that this result was driven by reductions of both appropriate and inappropriate shocks. Importantly these reductions were confirmed also comparing CRT-D patients with permanent AF treated by AVJA vs. CRT-D patients in sinus rhythm. Moreover also the annual rates of appropriate or inappropriate detections and ATP resulted significantly reduced by AVJA compared with AF patients treated with rate control agents and with SR patients.

These findings are of particular relevance, given that no randomized controlled trial have compared AVJA and rate control drugs strategies in CRT-D recipients, although the prevalence of permanent AF in such CRT population approaches 25% (24-25). So far only some observational studies (11-12, 18) and two meta-analyses (26-27) have evaluated these two rate control strategies and have suggested that for CRT patients with AF, AVJA is associated with better clinical outcome and a >50% reduction in all-cause mortality, compared with rate-slowing drugs. It is on this basis that both the European Society of Cardiology (ESC) and the American Heart Association guidelines (28-29) now consider patients with HF and permanent AF as candidates for CRT (Class IIa, level of evidence B), provided 100% of biventricular pacing is obtained, and, if not, AVJA should be considered. Our data on the incidence and burden of arrhythmic events adds new insight and provide further evidence of the benefit associated with AVJA in AF patients treated with CRT.

In this analysis patients with permanent AF and treated by AVJA were almost free from inappropriate VT/VF detections induced by AF; the few cases observed were probably associated to patients in which AV Junction ablation or modulation was not complete.

The fact that AVJA may reduce AF-related inappropriate ICD detections and therapies may be expected but at the best of our knowledge it has not been described so far.

The observation that AVJA may reduce also appropriate ICD detections and therapies is an important and intriguing finding that we associate with the known fact that patients with low ejection fraction during rapid AF may suffer VT/VF episodes and with the fact that rapid AF often negatively impact on CRT, by reducing biventricular pacing, and therefore worsen patient status; indeed Hayes et al. (30) in a large cohort of 36,935 CRT patients followed up in a remote-monitoring network showed that AF significantly limits the capability to perform cardiac resynchronization and that a biventricular pacing higher than 98% of all ventricular beats is associated with mortality reduction.

The observation that also patients classified in the SR group had higher incidence of both AF-related inappropriate ICD detection and therapies and appropriate ICD detection and therapies may be explained by the fact that paroxysmal AF is a frequent comorbidity of CRT patients and that new-onset AF is also a frequent finding in the follow-up of this patient population.

Clinical outcomes

Our data confirm that AVJA significantly reduces all-cause and HF hospitalizations. This finding favorably compares with the results of previous studies and meta-analyses (11-12, 18, 26-27) which showed reduced mortality in patients treated by AVJA compared with patients treated by rate control agents.

It is important to outline that the reduction of ICD therapies, particularly of ICD shocks, has usually a positive impact on patient's quality of life and therapy acceptance and may improve patient health; indeed several authors have hypothesized that ICD shocks are causally associated with poor prognosis. (31-32)

Clinical implications

Despite AVJA is indicated in AF CRT patients by both European Society of Cardiology and the American Heart Association guidelines (28-29) to provide 100% biventricular pacing, AVJA is still underused, likely because this practice makes patients pacemaker dependent. Several observational studies (11-12, 18) and two meta-analyses (26-27) have shown that, in CRT patients with AF, AVJA is associated with better clinical outcomes in terms of improved reverse remodeling, work capacity and survival, compared with rate-slowing drugs. Our data now show that AVJA in AF CRT patients is associated with a clinically significant reduction of ICD therapies. Importantly the observation of a lower incidence of appropriate episodes, associated with a lower incidence of ICD shocks and reduced occurrence of all-cause and HF hospitalizations, suggests that AVJA may determine an improved prognosis in these patients.

In our opinion compelling evidence has therefore been accumulated to reinforce the use of AVJA in patients with permanent AF indicated to CRT therapy.

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 we gathered data. Therefore there may be confounding factors associated, for example, with possible differences in the patients' populations or in the follow-up timing between the three projects from which we gathered data. We tried to optimize scientific methodology by pre-specifying analyses objectives before dataset opening and by correcting arrhythmic events risk for most important patients' characteristics, in particular for those which differed among analyzed groups. Moreover a homogeneous review of ICD detections and therapies was performed in all patients groups by a blind ERC. (20)

Conclusions

CRT-D patients with permanent AF have lower rate and incidence of ICD shocks, ATP and detections, both appropriate and inappropriate, when treated with AVJA compared with rate control agents. Moreover AVJA is associated to a lower incidence of all-cause and HF hospitalizations.

Further randomized studies on the role of AVJA in patients with AF undergoing CRT are warranted.

Author Contributions

Dr Gasparini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gasparini, Boriani, Proclemer, Lunati, Grammatico.

Acquisition of data: Gasparini, Kloppe, Lunati, Anselme, Landolina, Ferrer, Proclemer, Morani, Biffi, Ricci, Rordorf, Boriani.

Analysis and interpretation of data: Gasparini, Boriani.

Drafting of the manuscript: Gasparini, Boriani.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Mangoni

Administrative, technical, or material support: Manotta.

Project supervision: Proclemer, Lunati, Gasparini, Landolina, Biffi, Ricci, Rordorf, Morani.

Conflict of Interest and Disclosures

Dr Gasparini reports serving on the advisory board for Medtronic and Boston Scientific. Dr Proclemer reports serving on the advisory board for Medtronic. Dr Kloppe reports serving as speaker for Medtronic. Dr Martınez-Ferrer reports serving as lecturer and consultant for Medtronic. Dr Lunati reports serving as a consultant for Medtronic, Sorin, Boston SCI, and St Jude Medical.

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Figure legends

Figure 1. Number of patients in each research group and number of patients with ICD detection, ATP and shocks, overall and for appropriate and inappropriate episodes respectively

Figure 2. Incidence rate ratio and annual rate of all-cause ICD shocks, appropriate ICD shocks and inappropriate ICD shocks comparing AF+AVJA patients vs. AF+Drugs patients (section A), comparing AF+AVJA patients vs. SR patients (section B), and comparing AF+Drugs patients vs. SR patients (section C)

Figure 3. Time to first all-cause ICD shock (section A), first appropriate ICD shock (section B) and first inappropriate ICD shock (section C)

Table I : Baseline characteristics according to patient group

Patient Characteristics	SR (N = 2694)	AF+Drugs (N = 402)	AF+AVJA (N = 262)	p value	Post-hoc comparisons *
Demographics					
Age at first implant	66 ± 10	69 ± 9	69 ± 10	<0.001	1,3
Male	79.8%	87.3%	83.8%	0.001	1
Medical history					
Ischemic	53.3%	44.1%	43.0%	<0.001	1, 3
AMI	49.1%	40.9%	33.2%	<0.001	1, 3
NYHA III-IV	67.9%	68.4%	76.8%	0.015	
Ventricular	36.5%	32.7%	31.7%	0.15	
VF/Flutter	5.0%	6.3%	5.3%	0.56	
LBBB	58.1%	53.0%	40.4%	<0.001	2, 3
QRS ≥ 120 ms	92.8%	85.8%	78.7%	<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 (dl)	154 ± 60	141 ± 60	132 ± 61	<0.001	1, 3
LVEDV (dl)	206 ± 72	200 ± 75	181 ± 60	<0.001	3

AVJA=atrioventricular junction ablation, SR=sinus rhythm, AF=atrial fibrillation, AMI=acute myocardium infarction, NYHA=New York Heart Association, VF= ventricular fibrillation, LBBB=left bundle branch block, LVEF=left ventricle ejection fraction, LVESD=left ventricle end systolic diameter, LVEDD=left ventricle end diastolic diameter, LVESV=left ventricle end systolic volume, LVEDV=left ventricle end diastolic volume,

** Post-hoc comparisons are as follows: 1) SR vs. AF+Drugs; 2) AF+AVJA vs. AF+Drugs; 3) SR vs. AF+AVJA.*

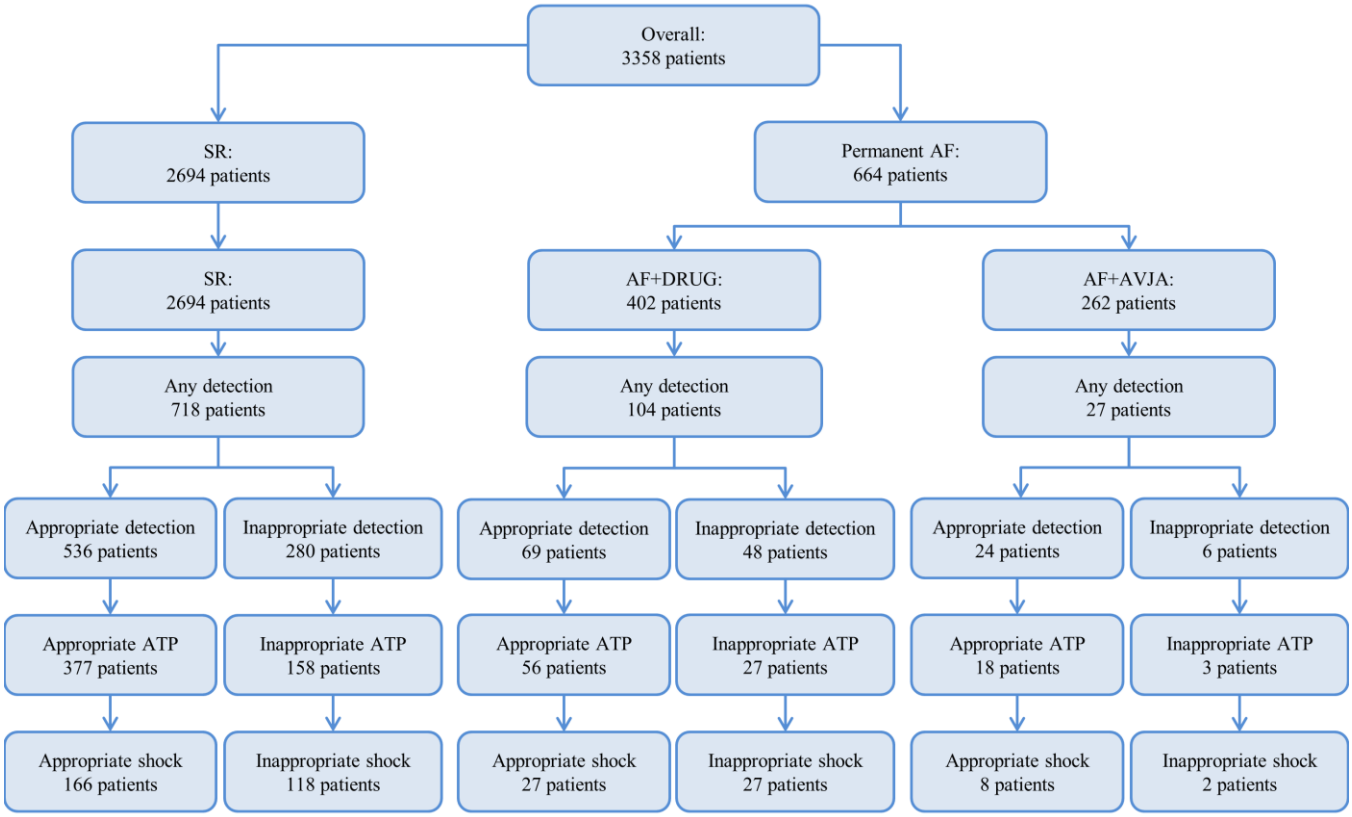
Table II : All-cause hospitalizations

Rhythm group	Patients with all-cause hospitalization	All-cause hospitalizations (n)	All-cause hospitalization annual rate * 100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	557 (20.7%)	808	24.4 (24.1 - 24.6)		
AF+DRUG	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

Table III : HF hospitalizations

Rhythm group	Patients with HF hospitalization	HF hospitalizations (n)	HF hospitalizations annual rate * 100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	191 (7.1%)	265	8.0 (7.9-8.1)		
AF+DRUG	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

Figure 1



AF = atrial fibrillation; AVJA = atrioventricular junction ablation; SR = sinus rhythm

Figure 2

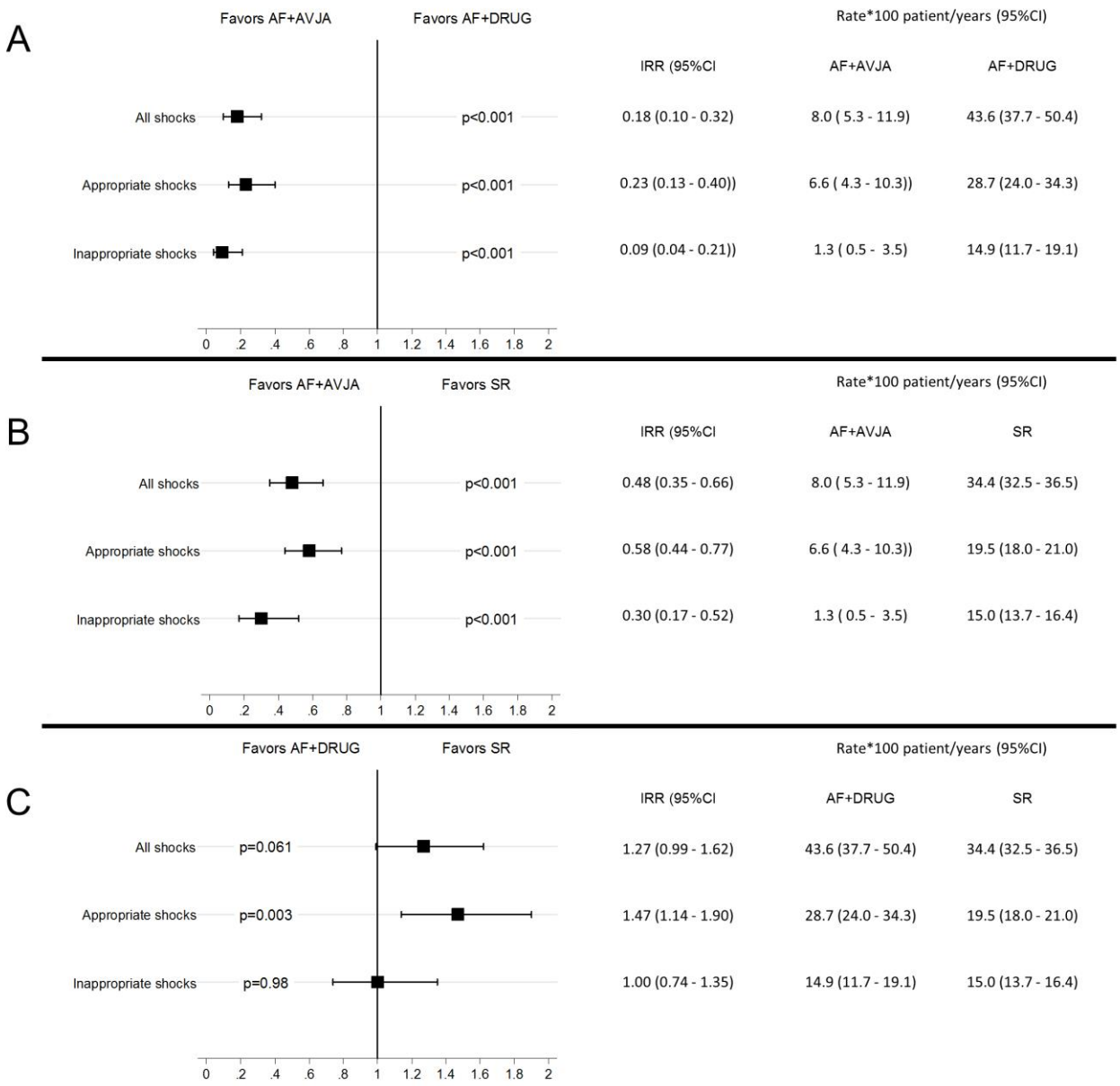
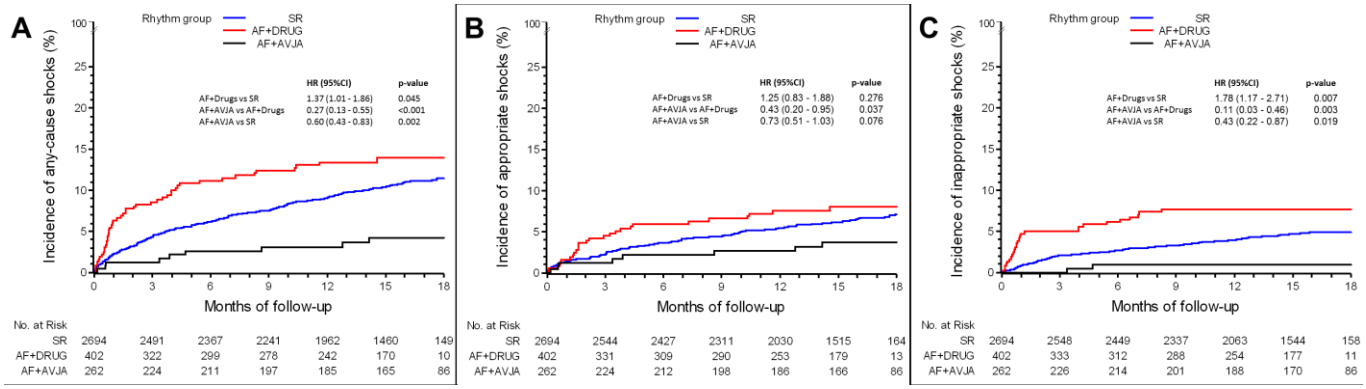

A
Favors AF+AVJA
Favors AF+DRUG
Rate*100 patient/years (95%CI)
IRR (95%CI
AF+AVJA
AF+DRUG
All shocks
p<0.001
0.18 (0.10 - 0.32)
8.0 (5.3 - 11.9)
43.6 (37.7 - 50.4)
Appropriate shocks
p<0.001
0.23 (0.13 - 0.40))
6.6 (4.3 - 10.3))
28.7 (24.0 - 34.3)
Inappropriate shocks
p<0.001
0.09 (0.04 - 0.21))
1.3 (0.5 - 3.5)
14.9 (11.7 - 19.1)
0 .2 .4 .6 .8 1 1.2 1.4 1.6 1.8 2
B
Favors AF+AVJA
Favors SR
Rate*100 patient/years (95%CI)
IRR (95%CI
AF+AVJA
SR
All shocks
p<0.001
0.48 (0.35 - 0.66)
8.0 (5.3 - 11.9)
34.4 (32.5 - 36.5)
Appropriate shocks
p<0.001
0.58 (0.44 - 0.77)
6.6 (4.3 - 10.3))
19.5 (18.0 - 21.0)
Inappropriate shocks
p<0.001
0.30 (0.17 - 0.52)
1.3 (0.5 - 3.5)
15.0 (13.7 - 16.4)
0 .2 .4 .6 .8 1 1.2 1.4 1.6 1.8 2
C
Favors AF+DRUG
Favors SR
Rate*100 patient/years (95%CI)
IRR (95%CI
AF+DRUG
SR
All shocks
p=0.061
1.27 (0.99 - 1.62)
43.6 (37.7 - 50.4)
34.4 (32.5 - 36.5)
Appropriate shocks
p=0.003
1.47 (1.14 - 1.90)
28.7 (24.0 - 34.3)
19.5 (18.0 - 21.0)
Inappropriate shocks
p=0.98
1.00 (0.74 - 1.35)
14.9 (11.7 - 19.1)
15.0 (13.7 - 16.4)
0 .2 .4 .6 .8 1 1.2 1.4 1.6 1.8 2

Figure 3


A
Rhythm group
SR
AF+DRUG
AF+AVJA
Incidence of any-cause shocks (%)
HR (95%CI) p-value
AF+Drugs vs SR 1.37 (1.01 - 1.86) 0.045
AF+AVJA vs AF+Drugs 0.27 (0.13 - 0.55) <0.001
AF+AVJA vs SR 0.60 (0.43 - 0.83) 0.002
Months of follow-up
No. at Risk
SR 2694 2491 2367 2241 1962 1460 149
AF+DRUG 402 322 299 278 242 170 10
AF+AVJA 262 224 211 197 185 165 86
B
Rhythm group
SR
AF+DRUG
AF+AVJA
Incidence of appropriate shocks (%)
HR (95%CI) p-value
AF+Drugs vs SR 1.25 (0.83 - 1.88) 0.276
AF+AVJA vs AF+Drugs 0.43 (0.20 - 0.95) 0.037
AF+AVJA vs SR 0.73 (0.51 - 1.03) 0.076
Months of follow-up
No. at Risk
SR 2694 2544 2427 2311 2030 1515 164
AF+DRUG 402 331 309 290 253 179 13
AF+AVJA 262 224 212 198 186 166 86
C
Rhythm group
SR
AF+DRUG
AF+AVJA
Incidence of inappropriate shocks (%)
HR (95%CI) p-value
AF+Drugs vs SR 1.78 (1.17 - 2.71) 0.007
AF+AVJA vs AF+Drugs 0.11 (0.03 - 0.46) 0.003
AF+AVJA vs SR 0.43 (0.22 - 0.87) 0.019
Months of follow-up
No. at Risk
SR 2694 2548 2449 2337 2063 1544 158
AF+DRUG 402 333 312 288 254 177 11
AF+AVJA 262 226 214 201 188 170 86

Appendix – Research Committees

Advance CRT-D Steering Committee

Frederic Anselme, Jacques Clementy, Maurizio Gasparini, Jose Bautista Martinez Ferrer, Massimo Santini, Jeorg O. Schwab

Advance III Steering Committee

ÁngelArenal, Maurizio Gasparini, A Hersi, Kloppe, Maurizio Lunati, Alessandro Proclemer, Jose Bautista Martinez Ferrer, M Wijffels

ClinicalService Scientific Committee

Mauro Biffi, Giuseppe Boriani, Maurizio Gasparini, Maurizizo Landolina, Maurizio Lunati, Alessandro Proclemer, Renato Ricci, Roberto Rordorf

Appendix – Research Participating Centres

IRCCS Humanitas Research Hospital – Rozzano (Milano); Ospedale Niguarda Ca Granda – Milano; Policlinico San Matteo – Pavia; Ospedale Civile Maggiore di Borgo Trento –Verona; Az. Ospedaliera S.Maria della Misericordia – Udine; Ospedale Mater Salutis di Legnago – Legnago; Ospedale San Filippo Neri (Roma); Ospedale Santa Maria Del Carmine - Rovereto (TM); A.S. Ospedaliera S. Croce e Carle – Cuneo; Ospedale San Raffaele – Milano; Villa S. Anna S.p.A. – Catanzaro; Klinikum Lüdenscheid (Lüdenscheid); Azienda Ospedaliera Sacro Cuore Don Calabria – Negrar; H. Txagorritxu (Vitoria); Hôpital Cardiologique (Bordeaux); Ist. Auxologico Italiano-Ospedale S.Luca – Milano; Ospedale Civile G. Mazzini – Teramo; Osp. S. Maria degli Angeli – Pordenone; Policlinico Sant Orsola-Malpighi – Bologna; Ente Ospedaliero Ospedali Galliera – Genova; Rheinische Friedrich-Wilhelm-Universität Bonn; Centre Hospitalier de Pau; Ospedale Santa Maria della Misericordia – Rovigo; Azienda Ospedaliera Careggi – Firenze; Ospedale SS. Antonio e Biagio – Alessandria; ULSS N.6 S. Bortolo – Vicenza; Ospedale San Carlo Borromeo – Milano;

Ospedale Humanitas Gavazzeni – Bergamo; Ospedale Luigi Sacco – Milano; Hôpital Michalon-CHU Grenoble; Ospedale San Gerardo – Monza; Ospedale S.Anna – Como; Ospedale Belcolle – Viterbo; H. Ramón y Cajal; Ospedale Loreto Mare – Napoli; AZ. Osp. Ordine Mauriziano Torino; Hospital de Santa Maria; UNITAS Hospital; Osp. S. Giovanni di Dio e Ruggi d'Aragona – Salerno; Hospital Universitario de Canarias; Azienda Ospedaliera Pugliese e Ciaccio – Catanzaro; Ospedale Civile dello Spirito Santo – Pescara; Hospital Clinico de Malaga - Virgen de la Victoria; Hôpital Charles Nicolle (Rouen); Azienza Ospedaliera Spedali Civili – Brescia; Az. Osp. Molinette S.Giovanni Battista – Torino; Ospedale Vito Fazzi – Lecce; Ospedale Sandro Pertini – Roma; Hospital General Universitario Gregorio Marañón (Madrid); Presidio ospedaliero C.e G. Mazzoni - Ascoli Piceno; Ospedale Misericordia e Dolce – Prato; King Khalid Univ. Hospital - King Saud University; Zentralklinik Bad Berka Kardiologie (Bad Berka); Hospital Ntra. Sra. de la Candelaria; Ospedale Civile di Conegliano - Conegliano Veneto; Diakoniekrankenhaus Rotenburg; Ospedale Civile – Asti; Ospedali Riuniti – Bergamo; Ospedale Sant Eugenio – Roma; St. Antonius Ziekenhuis Nieuwegein; CHU Hôpital Pasteur (Nice); Clinique Pasteur; Ospedale Civile G. Fornaroli – Magenta; Osp. San Giovanni Calibita Fatebenefratelli – Roma; A.O. Carlo Poma - Pieve di Coriano (MN); Ospedale Regionale San Maurizio – Bolzano; Azienda Ospedaliera San Salvatore – Pesaro; Az. Osp. Ca Foncello – Treviso; Medisch Spectrum Twente; Hôpital Trousseau (Tours); Ospedale S. Paolo P.M. – Milano; Azienda Ospedaliera Vittorio Emanuele Ferrarotto - S. Bambino (Catania); Ospedale Ferrarotto – Catania; NCN Nantes; Ospedale di Circolo - Desio (MI); Ospedale Fatebenefratelli e Oftalmico – Milano; Presidio Ospedaliero Riunito – Ciriè; P.O. di Montebelluna – Montebelluna; Nuovo Osp. Civile S. Agostino - Estense di Modena; Tyumen Cardiology Center; Hospital Universitario Virgen de las Nieves; CHU Nantes - Hôpital Guillaume et René Laënnec; Osp. S. Orsola-Fatebenefratelli – Brescia; Ospedale P. Cosma – Camposampiero; Casa di Cura Mater Domini – Castellanza; Hospital Virgen de La Salud; Hospital Clinico Universitario de Valencia; Ospedale di Circolo - Busto Arsizio (VA); Ospedale Civile di Mirano – Mirano; Ospedale Maggiore (Lodi); King Fahd Armed Forces Hospital; Hospital La Paz (Madrid); Hospital Virgen de las Nieves (Granada); CHU Hôpital de Pontchaillou Rennes; Sheba Medical

Center; Ospedale SS. Annunziata – Chieti; Ospedale Giovan Battista Grassi – Ostia; Hospital Geral de Santo António; Hopital St-Joseph; Chuvi-Xeral-Cíes; Hospital Universitario de San Juan; Centre Hospitalier Universitaire de Rennes; Hôpital Arnaud de Villeneuve (Cardiologie B) (Montpellier); Stab. Ospedaliero Di Summa-Perrino – Brindisi; Ospedale Civile - Legnano (MI); Centro Cuore Morgagni - Pedara (CT); Facoltà di Medicina e Chirurgia – Bari; Ospedale Bianchi-Melacrino-Morelli (Reggio Calabria); Hospital de Santa Marta; H. Germans Trias i Pujol (Badalona); Hôpital Arnaud de Villeneuve (Cardiologie A) (Montpellier); Hôpital Européen George Pompidou (Paris); Hôpital Henri Mondor (Créteil); Ospedale Civile - Arzignano (VI); Casa di Salute Montevergine - Mercogliano (AV); Ospedale L. P. Delfino ASL Roma G – Colleferro; Fond. Ist. S.Raffaele-G. Giglio – Cefalù; Policlinico Casilino – Roma; Azienda Ospedaliera di Padova – Padova; Ospedale S. Giacomo - Novi Ligure; Azienda Ospedaliera Maggiore della Carita (Novara); University of Cape Town - Groote Schuur Hospital; Universität Rostock– Medizinische Fakultät; Kliniken Essen Nordwest Philippusstift Krankenhaus (Essen); Hospital General Universitario de Alicante; Ospedale di Manerbio-Leno - Manerbio (BS); Ospedale S.Pietro Igneo - Fucecchio (FI); S. Maria Nuova Hospital - Reggio Emilia; Ospedale S. Donato (San Donato Milanese MI); Hospital Garcia Orta; SA; CHR La Citadelle Liege; CHU Brugmann; Klinikum Dortmund; Hospital General San Pedro de Alcantara; Hospital de Donostia; CH Rangueil Toulouse; Centre Hospitalier - Aix en Provence; Centre Hospitalier (La Rochelle); Semmelweis University AOK; Tel-Aviv Sourasky Medical Center (Tel-Aviv); Azienda Ospedaliera Carlo Poma – Mantova; Ospedale di Desenzano - Desenzano del Garda; Ospedale Maggiore - Policlinico – Milano; Ospedale Civile di Vimercate – Vimercate; Presidio Ospedaliero di Milazzo (AUSL 5) – Milazzo; Ospedale S. Maria delle Croci – Ravenna; Ospedale G. Moscati – Avellino; Azienda Ospedaliera Bolognini – Seriate; Fondazione Poliambulanza – Brescia; Azienda Ospedaliera G. Rummo; Osp. Villa San Pietro Fatebenefratelli – Roma; Ospedale S. Spirito - Casale Monferrato (Alessandria); Ospedale Policlinico A. Gemelli (Roma); Hospital Santa Maria (Lisbon); John Radcliffe (Oxford); AZ Nikolaas; CHR Namur; Universitätskliniken des Saarlandes; Kardiologisches Zentrum an der Klinik Rotes Kreuz; RWTH Aachen; Odense Universitets Hospital; Hospital General Yagüe; Hospital General de Ciudad Real;

Institut Arnaud Tzanck (St Laurent du Var); Hôpital de la Timone (Marseille); Hôpital Nord (St Etienne); Hôpital Lariboisière (Paris); Hôpital Béclère (Clamart); Sheba Medical Center; Ospedale di Circolo Galmarini - Tradate (VA); Ospedale Treviglio-Caravaggio - Treviglio (BG); Ospedale SS. Giacomo e Cristoforo – Massa; Osp. Santa Maria delle Grazie - Pozzuoli (NA); Ospedale San Vincenzo – Taormina; Casa di Cura Villa Verde – Taranto; A.U.S.L. - Osp. Guglielmo da Saliceto di Piacenza; Ospedale Oglio Po - Vicomoscano di Casalmaggiore; Presidio Ospedaliero di Venere - Bari Carbonara; Az. ULSS 12 Veneziana - Osp. Dell Angelo – Mestre.

Appendix – supplementary data

All-cause detections, ATP and shocks

TABLE 0:1 – ALL-CAUSE DETECTIONS

Rhythm group	Number of detection	Rate of detections * 100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	4205	127 (123 - 131)		
AF+DRUG	598	142 (131 - 153)	1.12 (0.90 - 1.39) vs. SR	0.32
AF+AVJA	154	51.1 (43.6 - 59.8)	0.63 (0.52 - 0.78) vs. SR 0.36 (0.24 - 0.53) vs. AF+DRUG	<0.001 <0.001

TABLE 0:2 – ALL-CAUSE ATP

Rhythm group	Episodes with ATP	ATP	Rate of ATP *100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	2865	3694	111 (108 - 115)		
AF+DRUG	421	521	123 (113 - 134)	1.11 (0.87 - 1.41) vs. SR	0.41
AF+AVJA	137	141	46.7 (39.6 - 55.1)	0.65 (0.52 - 0.81) vs. SR 0.38 (0.25 - 0.57) vs. AF+AVJA	<0.001 <0.001

TABLE 0:3 – ALL-CAUSE SHOCKS

Group	Number of episodes with all cause shocks	Rate of episodes with all cause shocks *100 patient years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	803	24.2 (22.6 - 25.9)		
AF+DRUG	147	34.8 (29.6 - 40.9)	1.44 (1.14 - 1.81) vs. SR	0.002
AF+AVJA	20	6.6 (4.3 - 10.3)	0.52 (0.39 - 0.69) vs. SR 0.19 (0.11 - 0.33) vs. AF+DRUG	<0.001 <0.001

Appropriate detections, ATP and shocks

TABLE 0:4 – APPROPRIATE DETECTIONS

Rhythm group	Number of appropriate detections	Rate of appropriate detections*100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	2993 (536)	90.3 (87.1 - 93.5)		
AF+DRUG	419 (69)	99.3 (90.2 - 109)	1.10 (0.87 - 1.40) vs. SR	0.44
AF+AVJA	140 (24)	46.4 (39.3 - 54.8)	0.70 (0.60 - 0.82) vs. SR 0.47 (0.32 - 0.69) vs. AF+DRUG	<0.001 <0.001

TABLE 0:5 – APPROPRIATE ATP

Rhythm group	Episodes with appropriate ATP	Appropriate ATP	Rate of appropriate ATP * 100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	2255	2883	86.9 (83.8 - 90.2)		
AF+DRUG	330	412	97.6 (88.6 - 107)	1.12 (0.87 - 1.45) vs. SR	0.38
AF+AVJA	132	136	45.1 (38.1 - 53.3)	0.72 (0.58 - 0.89) vs. SR 0.46 (0.31 - 0.69) vs. AF+DRUG	0.003 <0.001

TABLE 0:6 – APPROPRIATE SHOCKS

Group	Number of episodes with appropriate shocks	Rate of episodes with appropriate shocks *100 patient years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	498	15.0 (13.8 - 16.4)		
AF+DRUG	97	23.0 (18.8 - 28.0)	1.53 (1.19 - 1.96) vs. SR	<0.001
AF+AVJA	16	5.3 (3.2 - 8.7)	0.59 (0.45 - 0.78) vs. SR 0.23 (0.13 - 0.40) vs. AF+DRUG	<0.001 <0.001

Inappropriate detections, ATP and shocks

TABLE 0:7 – INAPPROPRIATE DETECTIONS

Rhythm group	Inappropriate Detections	Rate of inappropriate detections * 100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	1212	36.5 (34.5 - 38.7)		
AF+DRUG	179	42.4 (36.6 - 49.1)	1.16 (0.90 - 1.49) vs. SR	0.240
AF+AVJA	14	4.6 (2.7 - 7.8)	0.36 (0.24 - 0.53) vs. SR 0.11 (0.05 - 0.22) vs. AF+DRUG	<0.001 <0.001

TABLE 0:8 – INAPPROPRIATE ATP

Rhythm group	Episodes with inappropriate ATP	Inappropriate ATP	Rate of inappropriate ATP * 100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	610	811	24.5 (22.8 - 26.2)		
AF+DRUG	91	109	25.8 (21.4 - 31.2)	1.06 (0.79 - 1.41) vs. SR	0.71
AF+AVJA	5	5	1.7 (0.7 - 4.0)	0.26 (0.14 - 0.48) vs. SR 0.06 (0.02 - 0.18) vs. AF+DRUG	<0.001 <0.001

TABLE 0:9 – INAPPROPRIATE SHOCKS

Group	Number of episodes with inappropriate shocks	Rate of episodes with inappropriate shocks * 100 patient years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	305	9.2 (8.2 - 10.3)		
AF+DRUG	50	11.8 (9.0 - 15.6)	1.29 (0.98 - 1.69) vs. SR	0.067
AF+AVJA	4	1.3 (0.5 - 3.5)	0.38 (0.25 - 0.58) vs. SR 0.11 (0.05 - 0.24) vs. AF+DRUG	<0.001 <0.001

AF-related inappropriate detections, ATP and shocks

TABLE 0:10 – AF-RELATED INAPPROPRIATE DETECTIONS

Rhythm group	AF-related inappropriate detections	Rate of AF-related inappropriate detections*100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	935	28.2 (26.4 - 30.1)		
AF+DRUG	157	37.2 (31.8 - 43.5)	1.32 (1.03 - 1.69) vs. SR	0.028
AF+AVJA	12	4.0 (2.3 - 7.0)	0.38 (0.25 - 0.56) vs. SR 0.11 (0.05 - 0.23) vs. AF+DRUG	<0.001 <0.001

TABLE 0:11 – AF-RELATED INAPPROPRIATE ATP

Rhythm group	Episodes with AF-related inappropriate ATP	AF-related inappropriate ATP	Rate of AF-related inappropriate ATP * 100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	561	735	22.2 (20.6 - 23.8)		
AF+DRUG	89	107	25.3 (21.0 - 30.6)	1.14 (0.86 - 1.52) vs. SR	0.35
AF+AVJA	3	3	1.0 (0.3 - 3.1)	0.21 (0.10 - 0.45) vs. SR 0.04 (0.01 - 0.14) vs. AF+DRUG	<0.001 <0.001

TABLE 0:12 – AF-RELATED INAPPROPRIATE SHOCKS

Rhythm group	Episodes with AF-related inappropriate shocks	AF-related inappropriate shocks	Rate of AF-related inappropriate shocks *100 patient/years (95%CI)	Incidence rate ratio (95%CI)	p-value
SR	261	418	12.6 (11.5 - 13.9)		
AF+DRUG	37	49	11.6 (8.8 - 15.4)	0.92 (0.67 - 1.27) vs. SR	0.61
AF+AVJA	2	2	0.7 (0.2 - 2.7)	0.23 (0.11 - 0.48) vs. SR 0.06 (0.02 - 0.16) vs. AF+DRUG	<0.001 <0.001