Atrial Fibrillation in Recipients of Cardiac Resynchronization Therapy Device

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Abstract

Background: Atrial fibrillation (AF) is associated with increased morbidity and mortality in patients suffering from heart failure (HF). Patients in New York Heart Association (NYHA) HF classes III or IV, with systolic dysfunction and a wide QRS, are candidates for cardiac resynchronization therapy (CRT) and might benefit from overdrive atrial pacing (AOP).

Methods: The MASCOT trial enrolled 409 CRT device recipients (79% men), who were randomly assigned to AOP ON (n=197), versus AOP OFF (n=197) and followed for 1 year. Their mean age was 68±10 years, left ventricular (LV) ejection fraction (EF) 25±6%, QRS duration 163±29 ms. NYHA class III was present in 86% of patients and 19% had a history of paroxysmal AF. The primary study endpoint was incidence of permanent AF at 1 year.

Results: AOP increased the percentage of atrial pacing from 30 to 80% (*P*<0.0001), was well tolerated, and did not interfere with a) delivery of CRT (95% mean ventricular pacing in both groups), b) response to CRT (70% responders in the control, versus 67% in the treatment group), or c) cardiac function (LVEF increased from 24.5±6.2 % to 32.7±10.9 % in the control, and from 25.8±6.8% to 33.1±12.6 % in the treatment group). The incidence of permanent AF was 3.3% in both groups. By logistic regression analysis a history of AF (*P*<0.001), and absence of antiarrhythmic drugs (*P*=0.002) were associated with permanent AF.

Conclusions: In this first trial of a specific AF prevention algorithm in CRT recipients, AOP was safe and did not worsen HF. The prevention algorithm did not lower the 1-year incidence of AF.

Key Words: Cardiac resynchronization therapy - biventricular stimulation - multisite stimulation – heart failure – atrial fibrillation
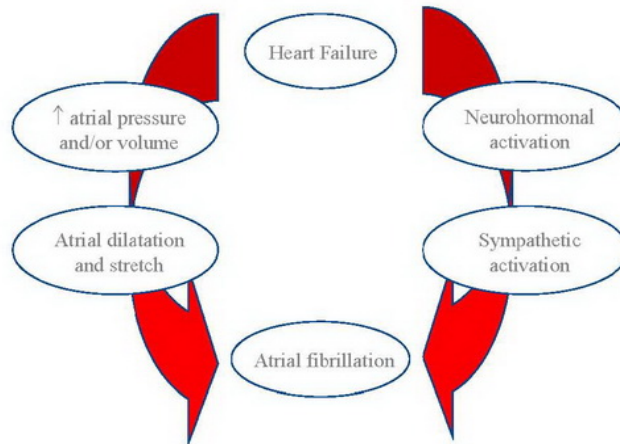
Introduction

Atrial fibrillation (AF), the most common sustained arrhythmia, and heart failure (HF), a leading cause of morbidity and mortality in developed countries, share several risk factors and often coexist in the same patient.[1,2] The prevalence of both disorders, each independently the cause of

considerable morbidity and mortality, is increasing. In addition, each appears to predispose directly to the other. Specifically, HF promotes atrial remodeling, and facilitates the development of AF,[3] while patients who develop AF in the midst of HF suffer from higher morbidity and mortality than patients who remain in sinus rhythm,[1,4] particularly in presence of left bundle branch block.[5] (Slide 1,2,3)
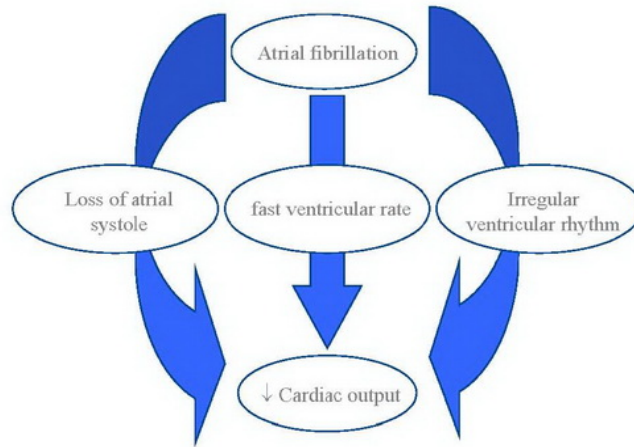
AF worsens CHF

Atrial fibrillation → Loss of atrial systole / fast ventricular rate / Irregular ventricular rhythm → ↓ Cardiac output
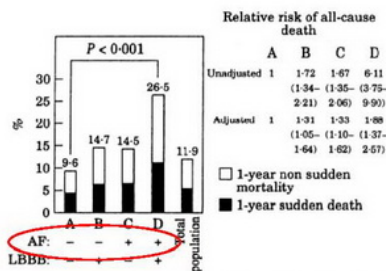

The presence of AF in CHF patients worsens their prognosis

Patients with both LBBB and AF have a worse 1-year mortality than other CHF patients.

Figure 1 One-year total mortality and sudden death in patients without complete left bundle-branch block (LBBB) and chronic atrial fibrillation (AF) (group A), with isolated left bundle-branch block (group B), with isolated chronic atrial fibrillation (group C) and simultaneous presence of complete left bundle-branch block and atrial fibrillation (group D).

Baldasseroni et al, EHJ 2002

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Cardiac resynchronization therapy (CRT) alleviates symptoms, decreases the need for hospitalizations, and improves cardiac function and survival in patients suffering from moderate to severe HF due to systolic dysfunction associated with electrical dyssynchrony.[6-9] In a few studies, CRT alone did not lower the incidence of AF,[10,11] while the episodes of AF resulted in a) loss of resynchronization or delivery of suboptimal therapy,[12,13] b) less reverse remodeling, and c) less improvement in functional capacity. Dedicated pacing algorithms have been designed to prevent AF by continuously overdrive pacing the right atrium above the intrinsic heart rate. (Slide 4)

MASCOT

AF Prevention by pacing: Background
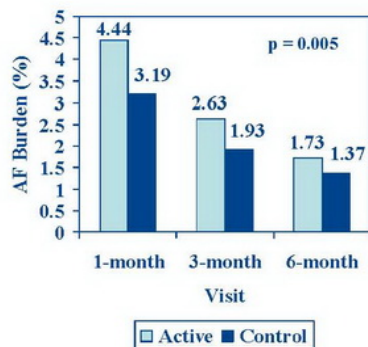
The ADOPT-A study demonstrated that the AF Suppression™ algorithm is safe and decreases symptomatic AF burden significantly in patients with sick sinus syndrome and AF at each follow up visit.

Carlson et al. J Am Coll Cardiol. 2003

These algorithms have been tested in various populations of paced patients with mixed results,[14-16] though not specifically in candidates for CRT.

The MASCOT trial was designed to examine whether adding atrial overdrive pacing (AOP) to biventricular stimulation has an effect on the incidence of permanent AF when compared with biventricular stimulation alone.[17]

Methods

Study design

This multicenter, single-blind, randomized, parallel study compared the safety and efficacy of a specific AOP algorithm (AF Suppression™, St Jude Medical, Sylmar, CA) in CRT recipients. The study protocol was reviewed and approved by the Institutional Ethics Committee of each participating centers, and all patients granted their informed consent. After successful CRT device implantation, and before hospital discharge, the patients were randomly assigned to AOP ON versus OFF for the duration of follow-up (NCT00187252).

Definitions

Patients were classified as having new-onset AF, if 1) they had no history of AF at entry into the study, and 2) developed AF documented on an electrocardiogram during follow-up, or during an adverse event or hospitalization. This definition is similar to that by Hoppe et al. in the retrospective analysis of the CARE-HF data set.[10] Permanent AF was defined as long-standing AF for which cardioversion was not indicated or attempted, as described in the North American and European professional guidelines for the management of patients with AF.[18]

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Study endpoints

MASCOT - Study endpoints

Primary:
• Reduction in the incidence of permanent Atrial Fibrillation at 12 and 24 months.

Secondary:
• Incidence of new-onset AF;
• Changes in LVEF, LVESD, LVEDD;
• Changes in NYHA functional class;
• Changes in quality of life;
• Mortality.

The primary endpoint was incidence of permanent AF over 12 months of follow-up. The secondary endpoints were 1) incidence of new-onset AF, 2) changes in left ventricular (LV) ejection fraction (EF) and dimensions, 3) changes in New York Heart Association (NYHA) functional class and quality of life (QOL), assessed by the Minnesota Living With Heart Failure® questionnaire, and 4) mortality.

Cardiac resynchronization therapy systems

All patients underwent implantation of a Frontier™ or Frontier II CRT-P device, or of an Epic™ HF or Atlas™ HF CRT-D device (St Jude Medical). All devices include the AF Suppression™ algorithm. The OAP function increases the pacing rate when 2 intrinsic atrial events are detected within 16 cycles. Once stable pacing is achieved, the system paces at the overdrive rate for 15 cycles. If, during a period of OAP, intrinsic P waves are detected, the algorithm increases the pacing rate again to a maximum of 110 ppm. If no intrinsic P wave is detected during OAP, the algorithm lengthens the interval between consecutive paced events, gradually slowing the pacing rate to the programmed base rate, or to the sensor-defined rate.

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Patient selection and randomization

Patients were eligible for enrollment if they fulfilled the following criteria: 1) NYHA HF functional class III or IV despite optimal medical therapy, 2) QRS duration ≥130 ms, 3) LVEF ≤35%, 4) LV end-diastolic diameter ≥55 mm. Exclusion criteria were 1) permanent AF, 2) myocardial infarction, cardiac surgery or a coronary revascularization procedure within the previous 3 months, 3) <6 months life expectancy due to a disorder other than CHF, or pregnant state.

Random assignment of the patients to the treatment versus the control group was performed and coordinated centrally by the study sponsor.

Sample size calculation

At least 379 patients needed to be enrolled in the study to detect a 6.2% absolute reduction in the development of permanent AF between the control and treatment groups, assuming a 1-sided, 5% significance level, with an 80% power.

Statistical analyses

All analyses were based on the intention-to-treat principle. Data collected in the 2 groups were compared at 12 months. Normality of the data was verified using box-and-whisker, normal probability plots and Kolmogorov-Smirnov tests for normality. Continuous variables from the normal distribution were compared using the two-sample *t*-test for independent variables. Non-parametric Wilcoxon-Mann-Whitney and Wilcoxon-signed-rank tests were used for non-normal variables. Exploratory logistic regression analyses were carried out to estimate the extent to which selected variables were independently associated with the development of permanent AF, and death from all causes. A *P* value <0.05 was considered significant.

Results

Between September 2003 and March 2006, 409 patients were enrolled in the MASCOT trial, at 34 medical centers, in 10 countries. Their mean age was 68±10 years, mean LVEF 25±6%, 203 patients (49.6%) suffered from ischemic heart disease, 350 (85.6%) were in NYHA functional class III, and 78 patients (19%) had a history of paroxysmal AF. Baseline characteristics of the study population are listed in slides 6,7,8,9. Over 90% of patients were treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, or a diuretic, or both, 72% with a beta-adrenergic blocker and 29% with an antiarrhythmic drug.

MASCOT – Baseline characteristics (2)

	TOTAL (n=409)
Heart rate (bpm)	71 ± 7
Systolic BP (mm Hg)	119 ± 18
Diastolic BP (mm Hg)	71 ± 11
LVEF (%)	25 ± 6
LVESD/DD (mm)	$60 \pm 10 / 70 = 10$
LVESV/DV (ml)	$164 \pm 68 / 222 \pm 81$
LA diameter (mm)	47 ± 9
Hypertension (%)	43
Diabetes (%)	29

MASCOT – AOP ON vs. OFF

	OFF (n=197)	ON (n=197)
Male (%)	80	79
Ages (years)	68 ± 9	68 ± 10
NYHA Class III (%)	88	84
Ischemic (%)	51	47
AF History (%)	17	19
QRS width (ms)	162 ± 26	166 ± 32
QoL	46 ± 22	43 ± 20
LVEF (%)	25 ± 6	26 ± 7

All p-values between the 2 groups non significant

MASCOT

MASCOT – Response to AOP

	AOP OFF	AOP ON	
% atrial pacing	30±33	80±29	P<0.0001
% ventricular pacing	95±10	95±14	P=ns
Heart rate (bpm)	67±11	72±13	P=0.05

The AOP algorithm was turned OFF in 13 patients, because of permanent AF (2 pts), atrial lead displacement (2 pts), high atrial threshold and risk of early battery depletion (4 pts), and intolerable palpitations/atrial tachyarrhythmias in (5 pts).
It was turned ON in 1 patient suffering from paroxysmal AF.

MASCOT

MASCOT – Response to CRT

	AOP OFF		AOP ON	
	Baseline	1 year	Baseline	1 year
% of pts who improved ≥ 1 NYHA class	N/A	70	N/A	67
LVEF (%)	24.5±6.2	32.7±10.9*	25.8±6.8	33.1±12.6*
LVESD (mm)	60±10	53±13*	60±10	57±14*
QoL	46±22	24±20*	43±20	25±20*

* *p<0.0001* compared to baseline

There are no differences between groups at 1-year.

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CRT devices were successfully implanted in 394 patients. The choice of device was left to the investigators. CRT-D devices were implanted in 228, and CRT-P devices in 174 patients. The right atrial lead was implanted in the appendage in 91% of patients, 81% of the RV leads were placed at the apex, and 69% of the LV leads were implanted in a lateral or postero-lateral position. These 394 patients were randomly assigned to AOP OFF (control group – n=197) versus AOP ON (treatment group – n=197). The baseline characteristics of the 2 study groups were similar. At 1 year, 323 patients remained in the study, of whom 148 patients in the control group and 156 in the treatment group attended the 12-month follow-up visit. The flow of patients through the course of the study is shown in slide 10.
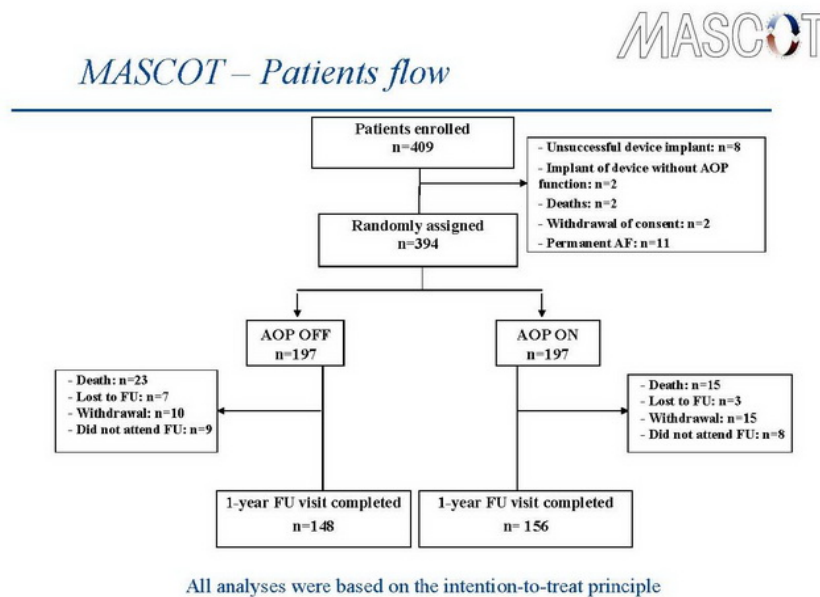

Response to cardiac resynchronization therapy

In both study groups, CRT produced changes consistent with considerable improvements in cardiac function and mitigation of HF manifestations. (Slide 11) The NYHA class decreased by ≥1 class in 70% of patients in the control group versus 67% of patients in the treatment group. Similarly, the Quality Of Life (QOL) score decreased (indicating an improvement in QOL) from 46±22 to 24±20 in the control group (*P*<0.0001) and from 43±20 to 25±20 in the treatment group (*P*<0.0001). The LV end-systolic diameter decreased from 60±10 mm to 53±13 mm in the control

group, and from 60±10 mm to 57±14 mm in the treatment groups (both *P*<0.0001), while LVEF increased from 24.5±6.2 % to 32.7±10.9 % in the control group, and from 25.8±6.8% to 33.1±12.6 % in the treatment group (both *P*<0.0001). The between-groups differences in these measurements at 1 year were not statistically significant.
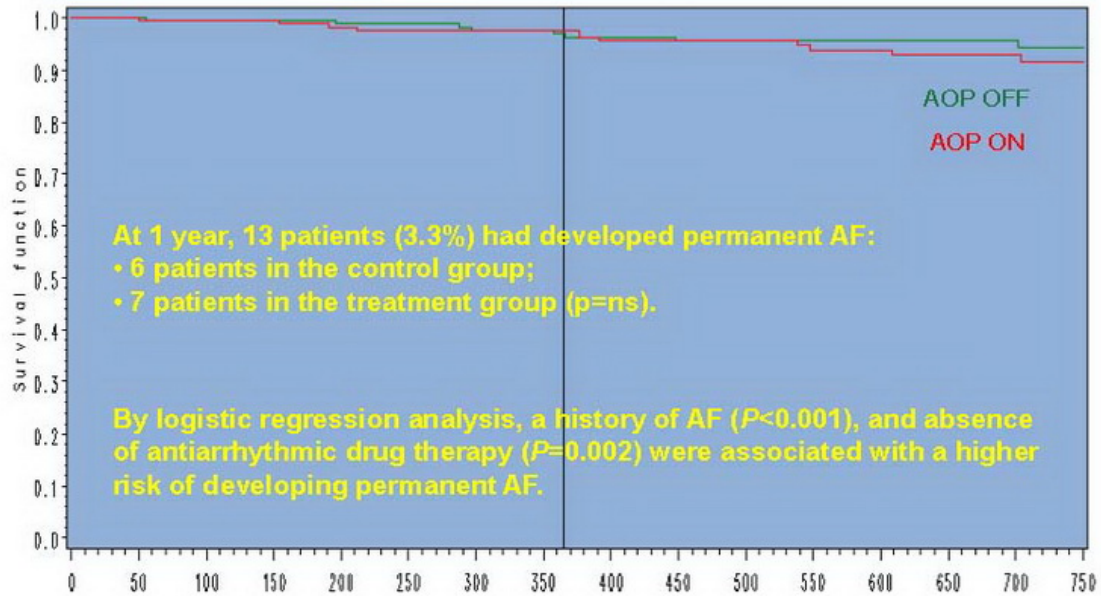
MASCOT – New onset AF
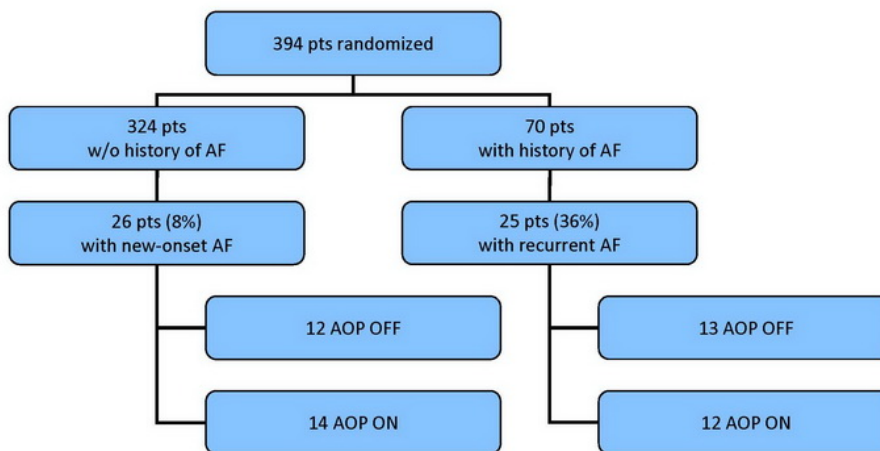
Effect of atrial overdrive pacing

The mean percentage of atrial pacing was 80±29% in the treatment, versus 30±33% in the control group (*P*<0.0001). Respective mean percentages of ventricular pacing were 95±14% versus 95±10% (ns), as expected in recipients of CRT devices. The mean heart rate was 67±11 bpm in the control group versus 72±13 bpm in the treatment group (*P*=0.05) (Slide8). The atrial overdrive algorithm was turned OFF during follow-up in 13 patients, because of permanent AF in 2 patients, atrial lead displacement in 2, high atrial threshold and risk of early battery depletion in 4, and intolerable palpitations/atrial tachyarrhythmias in 5 patients. It was reprogrammed from OFF to ON in 1 patient suffering from paroxysmal AF.

At 1 year, permanent AF had developed in 13 patients (3.3%): 6 patients in the control group, versus 7 patients in the treatment group (ns) (slide 12).

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MASCOT – Incidence of permanent AF

At 1 year, 13 patients (3.3%) had developed permanent AF:
- 6 patients in the control group;
- 7 patients in the treatment group (p=ns).

By logistic regression analysis, a history of AF ($P<0.001$), and absence of antiarrhythmic drug therapy ($P=0.002$) were associated with a higher risk of developing permanent AF.

Among 324 patients without history of AF, 26 (8%) developed new-onset AF, including 20 patients with paroxysmal and 6 with permanent AF. New-onset AF developed in 12 patients in the control group, versus 14 patients in the treatment group (ns) (Slide 14). Among 70 patients with a history of AF at baseline, 25 had recurrences of AF during follow-up, permanent in 7 patients. Recurrent AF was documented in 13 patients in the control group, versus 12 patients in the treatment group (ns).

MASCOT – New onset AF
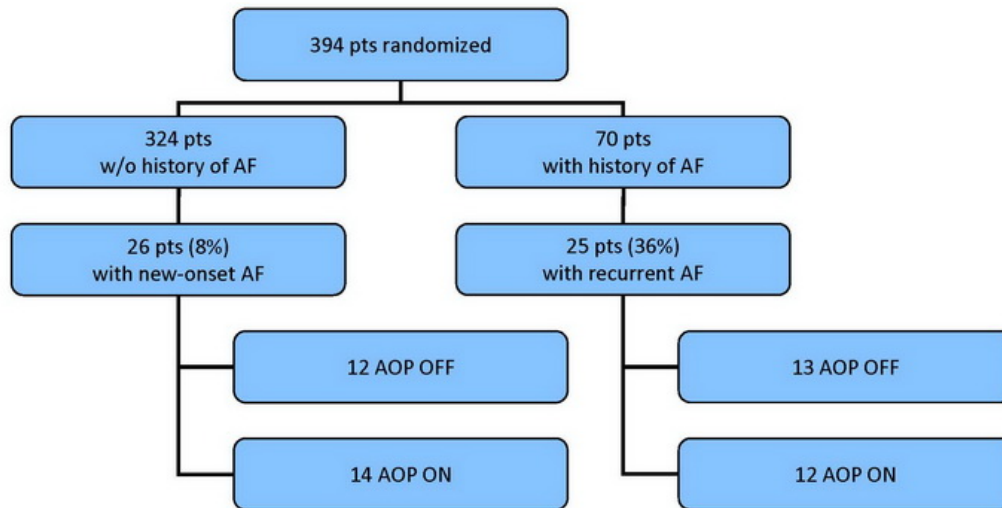
By logistic regression analysis, a history of AF (*P*<0.001), and absence of antiarrhythmic drug therapy (*P*=0.002) were associated with a higher risk of developing permanent AF.

Deaths during follow-up

During the 1-year follow-up period, 38 patients (9.6%) died, including 23 patients (11.7%) in the control and 15 patients (7.6%) in the treatment group, a statistically non-significant difference (slide 15). The causes of death were cardiac in 23, non-cardiac in 9 and from unknown causes in 6 patients By logistic regression analysis, ischemic heart disease as the cause of HF (*P*=0.04), a history of AF (*P*=0.03), male gender, (*P*=0.03), and increasing NYHA functional class (*P*=0.02) were associated with a higher risk of death.

MASCOT – Mortality
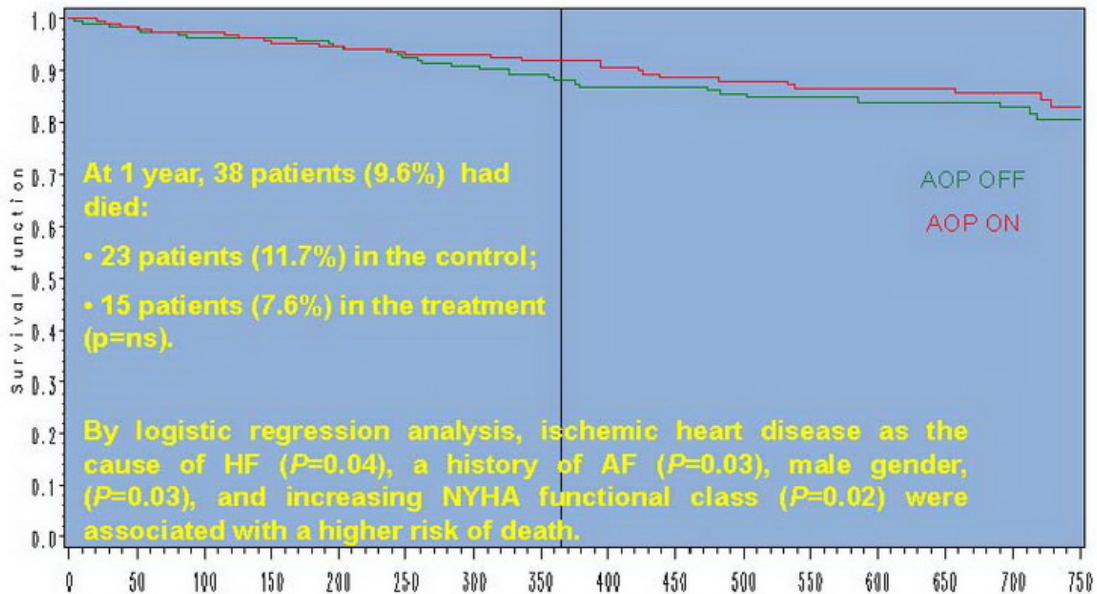
Discussion

MASCOT is the first trial that prospectively evaluated the incidence of permanent and non-permanent AF, and the possible preventive benefit conferred by AOP, in a population of CRT recipients. A few small, retrospective studies[11,19,20] and a *post hoc* analysis of the CARE-HF trial[10] have examined the effects of CRT on the development of AF, while the prevention of AF in CRT recipients has not been studied. The baseline characteristics of the patients enrolled in MASCOT, similar to the patients enrolled in CARE-HF, are representative of CRT candidates. Fung et al. compared the incidence of new-onset AF in patients managed with CRT and in a matched control group over a period of 3 years.[20] The annual incidence of new-onset AF, detected during hospital visits by clinical evaluations, was 2.8% in recipients of CRT devices, versus 10.2% in the control group, suggesting a preventive effect of CRT against AF. Huegl et al. observed a decrease in AF burden detected by device diagnostics, during the first 3 months following device implantation, in a small group of CRT device recipients.[19] In that study, the occurrence of AF was neither related to a previous history of AF, not interfered with the response to CRT. Using device diagnostics,

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Adelstein et al. compared a group of patients who underwent unsuccessful implantation of CRT devices, to CRT device recipients who did or did not respond to resynchronization therapy.[11] During a 1-year follow-up, a difference in the incidence of AF was observed neither between controls and CRT device recipients, nor between responders and non-responders to CRT.

In a *post hoc* analysis of the CARE-HF study,[10] the prevalence of AF in the group managed with CRT was 19% at baseline, and new-onset AF developed in 16% over the 29 months of follow-up. CRT did not affect the development of AF and, conversely, AF did not negate the therapeutic effects of CRT. In an unpublished analysis of the COMPANION trial, the prevalence of AF at baseline was 17% and the incidence of new-onset AF was 16% over 15 months.[21] In that study, compared to optimal pharmacological treatment, CRT did not lower the incidence of AF detected by clinical evaluations during hospital visits. Finally, in a study of 319 paced patients with histories of AF, Carlson et al. observed a 25% relative reduction in symptomatic AF burden by AOP compared with conventional pacing.[14]

In MASCOT, based on a review of medical files, the prevalence of AF at baseline was 19%, the 1-year incidence of new-onset AF was 8%, and the incidence of permanent AF was 3.3%. A history of AF and the absence of antiarrhythmic drugs at the time of inclusion in the study were associated with the development of permanent AF. The programming of AOP was well tolerated and increased the percentage of atrial pacing significantly, from 30% to 80%, while increasing the mean heart rate only slightly. However, in contrast to its effects in paced patients with sinus node disease,[14] enabling this function in this study had no effect on the incidence of permanent or new-onset AF. Neither AOP, nor the development of permanent or new-onset AF interfered with the response to CRT.

All CRT studies have been performed with atrial tracking, biventricular pacing (VDD mode), resulting in absence of atrial pacing. In practice, most devices are programmed in DDD mode, resulting in atrial pacing when the intrinsic heart rate falls below the programmed back up rate. This enables the optimization of drug therapy, including the prescription of beta-adrenergic blockers.[22,23] In this trial, the percentage of atrial pacing in the control group was 30%. The effect of this percentage of atrial pacing on the development of AF is unknown, and may have interfered with the study results.

The results of our of multiple variable versus mortality analysis are concordant with the observations made by Gasparini et al.,[32] who found that HF due to ischemic heart disease and

NYHA functional class IV predicted an increased mortality. The possible impact of a history of AF on mortality confirms the need to further investigate the development of AF in patients suffering from HF.

Limitations of our study

The incidence of AF was measured on the basis of clinical information available during hospital visits. The low incidence of permanent AF, which did not allow testing of the primary endpoint of the study, is another important limitation. Whether this low incidence of AF results from possible beneficial effect of CRT is uncertain.

Conclusions

The results of this first trial of AF prevention in recipients of CRT devices showed that AOP was safe in patients suffering from HF and depressed ventricular function. While the algorithm effectively increased the percentage of atrial pacing from 30% to 80%, it did not lower the incidence of permanent AF over a 1-year follow-up. The patients will be followed for another year to confirm these results. (Slide 16)

MASCOT – Conclusions

The MASCOT study is the 1st study that investigated prospectively the development of AF in CRT patients.

The incidence of permanent AF is much lower that expected in the CRT population (3.3%) and thus the efficacy of atrial overdrive pacing could not be assessed.

AOP appears to be safe and well tolerated by heart failure patients and does not impair the response to CRT.

AOP should be switched OFF to save battery energy and could be turned ON based on device diagnostics and patient symptoms in case of atrial tachyarrhythmias.

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