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FASTTRACK CLINICAL RESEARCH
Atrial fibrillation

A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS

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Aims We tested the hypothesis that atrioventricular (AV) junction ablation in conjunction biventricular pacing [cardiac resynchronization (CRT)] pacing is superior to pharmacological rate-control therapy in reducing heart failure (HF) and hospitalization in patients with permanent atrial fibrillation (AF) and narrow QRS.

Methods and results We randomly assigned 102 patients (mean age 72 ± 10 years) with severely symptomatic permanent AF (>6 months), narrow QRS (≤110 ms), and at least one hospitalization for HF in the previous year to AV junction ablation and CRT (plus defibrillator according to guidelines) or to pharmacological rate-control therapy (plus defibrillator according to guidelines). After a median follow-up of 16 months, the primary composite outcome of death due to HF, or hospitalization due to HF, or worsening HF had occurred in 10 patients (20%) in the Ablation+CRT arm and in 20 patients (38%) in the Drug arm [hazard ratio (HR) 0.38; 95% confidence interval (CI) 0.18–0.81; $P = 0.013$]. Significantly fewer patients in the Ablation+CRT arm died from any cause or underwent hospitalization for HF [6 (12%) vs. 17 (33%); HR 0.28; 95% CI 0.11–0.72; $P = 0.008$], or were hospitalized for HF [5 (10%) vs. 13 (25%); HR 0.30; 95% CI 0.11–0.78; $P = 0.024$]. In comparison with the Drug arm, Ablation+CRT patients showed a 36% decrease in the specific symptoms and physical limitations of AF at 1 year follow-up ($P = 0.004$).

Conclusion Ablation+CRT was superior to pharmacological therapy in reducing HF and hospitalization and improving quality of life in elderly patients with permanent AF and narrow QRS.

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Keywords Atrial fibrillation • Heart failure • Cardiac resynchronization therapy • Catheter ablation • AV node ablation • QRS width

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Introduction

There is sufficient evidence of the efficacy of atrioventricular (AV) junction ablation plus right ventricular (RV) pacing in improving the symptoms of high heart rate and exercise tolerance in patients with atrial fibrillation (AF). By contrast, most studies and meta-analyses have yielded neutral results regarding the progression of heart failure (HF), hospitalization, and mortality,[1–11] with one exception.[12]

The downside is that, in patients with native narrow QRS, the non-physiological RV pacing is reported to induce left ventricular (LV) dyssynchrony in about 50% of cases,[13,14] which may be followed by symptoms of worsening of HF. Indeed, on RV pacing, the ventricular activation sequence resembles that of left bundle branch block, i.e. the LV septum is activated before the LV free wall. Cardiac resynchronization therapy (CRT) may prevent the potential LV dyssynchrony induced by RV pacing and therefore appears to be an interesting approach in patients eligible for AV junction ablation.

While there is a rationale for an additive effect of CRT to that of AV junction ablation, the benefit of this strategy, in comparison with that of pharmacological rate-control therapy, has never been studied in trials of patients with permanent AF and native narrow QRS. Narrow QRS (i.e. <120 ms) is a contraindication for CRT in patient with sinus rhythm.[15–17]

What we know from the literature is that CRT is better than RV pacing, after AV junction ablation, in heterogeneous AF populations, which have mainly included HF patients with wide QRS and depressed systolic function.[18–22] *Post hoc* analyses of small subpopulations have been unable to find differences in outcome between patients with narrow QRS and those with wide QRS, nor between patients with depressed ejection fraction (EF) and those with preserved EF, thus suggesting a similar benefit.[19,22] However, given the lack of a control group of patients without AV junction ablation, CRT could have simply counteracted the harmful effect of RV pacing without affecting the global outcome.

The need to compare pharmacological and non-pharmacological rate-control strategies constituted the rationale of the Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy (APAF-CRT) trial. The purpose of the APAF-CRT trial was to demonstrate the superiority of an approach consisting of AV junction ablation and CRT pacing over optimal pharmacological rate control in patients with permanent AF and narrow QRS regarding the progression of HF, hospitalization and mortality.

Methods

The APAF-CRT trial was a prospective, randomized, parallel, open-label clinical trial involving patients with severely symptomatic permanent AF and narrow QRS, and consisted of two specific consecutive (overlapping) phases, i.e. a morbidity trial and a mortality trial. The morbidity trial, which was conducted in 10 European general hospitals, was designed to test the hypothesis that AV junction ablation and biventricular pacing is superior to pharmacological rate-control therapy in reducing HF and hospitalization. Recruitment began in October 2014 and patients were followed up for a maximum period of 3 years, during which yearly visits were required. Additionally, symptomatic status was assessed at 1 year. Events were collected by investigators by means of a web-based electronic system and were finally adjudicated by an independent Clinical Events Committee, the members of which were blind to therapy assignment.

The study protocol was approved by the local ethics committee at each participating institution and complied with the provisions of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients

Patient inclusion criteria were as follows: (i) severely symptomatic permanent AF (>6 months) which has been considered unsuitable for AF ablation or in which AF ablation had failed; (ii) narrow QRS (i.e. ≤110 ms); and (iii) at least one hospitalization for HF in the previous year.

Patient exclusion criteria were as follows: (i) hospital New York Heart Association (NYHA) Class IV and systolic blood pressure ≤80 mmHg despite optimized therapy; (ii) severe concomitant non-cardiac disease; (iii) need for surgical intervention; (iv) myocardial infarction within the previous 3 months; (v) previously implanted devices.

Randomization and procedures

Patients were randomized in a 1:1 ratio to AV junction ablation and biventricular pacing (plus defibrillator according to guidelines) (Ablation and CRT arm) or optimal pharmacological rate-control therapy (plus defibrillator according to guidelines) (Drug arm). A randomly permuted-block randomization list was generated by computer at a central location and was stratified by centre and by baseline EF (≤35% and >35%).

Any commercially available CRT-P or CRT-D device was permitted. The RV lead was positioned in the RV apex. The LV lead was targeted to the basal-mid-portions of the free wall. The atrial port of the device was excluded. The final programming of the implanted device was left to the physicians' discretion. Defibrillator back-up was chosen at the discretion of the physicians according to the guidelines of the European Society of Cardiology (ESC).[15] System revision was recommended during all follow-up visits if persistent capture was not obtained.

In the ablation arm, right-sided AV junction ablation was attempted first; the left approach was added if right-sided ablation failed to achieve persistent third-degree AV block. Repeated ablation procedures were recommended during follow-up if regression of AV block had occurred.

Cardiac resynchronization therapy device implantation and ablation procedures were performed as soon as possible after randomization and within a maximum time of 30 days. Pharmacological HF therapy was optimized according to current guidelines in both arms. In the control arm, the rate-control therapy was optimized in order to achieve a resting heart rate <110 b.p.m.[23]

Outcomes

The primary outcome was a composite of death due to HF, or hospitalization due to HF, or worsening HF, whichever occurred first. Secondary clinical outcomes were total mortality, hospitalization for HF, and worsening HF. Hospitalization for HF was defined as a hospital admission that was associated with an overnight stay owing to the occurrence of increasing symptoms of congestive HF which necessitated a substantial increase in diuretics and/or appropriate treatment for uncontrolled intolerable AF-related symptoms. Worsening HF was defined as a worsening of signs and symptoms of congestive HF, i.e. documentation of worsening symptoms of shortness of breath at rest and during effort, effort intolerance or easy fatigue, and of objective signs of HF, which included data regarding volume retention, pulmonary rales and the need for adjunctive therapy, and/or the need for appropriate treatment for uncontrolled intolerable AF-related symptoms. Death due to HF was defined as death occurring in the context of clinically worsening symptoms and/or signs of HF without evidence of another cause of death.

The primary and secondary clinical outcomes were adjudicated by a Clinical Events Committee, whose members were unaware of the

patients' study-group assignments. The primary and secondary clinical outcomes were analysed according to the intention-to-treat (ITT) principle.

The tertiary outcome was quality of life, which was assessed at the baseline and during the 1 year follow-up visit. Quality of life was assessed by means of the European Heart Rhythm Association (EHRA) score[23] and the six-item Specific Symptom Scale (SSS) score. The physician-administered four-item EHRA score classifies AF symptoms as absent, mild, severe, or disabling.[23] The self-administered SSS was developed as a disease-specific instrument to measure the patient's perception of the frequency and severity of arrhythmia-related symptoms. This instrument has been demonstrated to discern changes in the symptoms of patients with AF, both in sequential and in case–control studies.[2,24] An on-treatment analysis was applied to quality of life scores.

Statistical analysis

Data analysis

In all analyses, we used a two-sided Type-1 error alpha = 0.05. Continuous data are shown as means ± standard deviation or medians (25th–75th percentile), as appropriate. Absolute and relative frequencies were used to compare categorical data. A paired Student's *t*-test was used to compare continuous variables, Fisher's exact test was used to compare proportions, and analysis of variance for repeated measures was used to compare treatment effect and EF effect within subjects. The Greenhouse-Geisser adjustment was applied to degrees of freedom, and equal weights were attributed to measurements. Patients who did not suffer a pre-specified event were censored at the last observation. For the ITT analysis of, the primary and secondary outcomes, the hazard ratio (HR) of treatment allocations were estimated by means of Cox's proportional hazard regression model, after checking for the assumption of proportionality. In addition, the primary and secondary outcomes were described by means of the Kaplan-Meier product-limit method and compared by means of the log-rank test. Sensitivity analyses were also performed. Analyses were performed by means of MedCalc version 15.8 (MedCalc Software, Mariakerke, Belgium) and IBM SPSS v.24 (IBM Software Group, Chicago, IL, USA).

Sample size justification

In the APAF trial,[22] 26% of patients in the control RV pacing arm reached the same combined Endpoint as that of this study at 12 months; CRT reduced this rate by 63%. Thus, in a prudential estimation which assumed that morbidity on drug therapy would be equal to that of RV pacing, 137 patients in each group would have 80% power to detect a 60% relative reduction in the primary composite outcome after a maximum follow-up of 3 years (accrual of 2 years) with a two-sided alpha of 5% and a common exponential dropout rate of 10%.

Interim analysis

In absence of historical data regarding the benefit of CRT pacing vs. rate-control drug therapy that could allow a more realistic sample size calculation, we planned an ad-interim analysis once 50% of the statistical information had been obtained. This was assumed to occur at 50% of patients, figure which is equivalent to 25 adjudicated primary outcome events. On 8 May 2018, following the interim analysis, the Clinical Events Committee informed the principal investigator that the difference observed between the two arms was very close to that specified in the 'stopping rule, recommended that the trial be terminated on account of the evident superiority of the results obtained in one of the arms, and selected 23 June 2018, as the cut-off date for all efficacy analyses; the sponsor accepted this decision. As per protocol, the investigators were informed that the study would continue after that date, in order to evaluate the mortality outcome (i.e. APAF Mortality trial).

Results

Patients

A total of 109 patients were randomized; 102 of these were finally included for analysis and assigned to the Ablation and CRT arm (50 patients) or to the Drug arm (52 patients) (*Figure 1*). The two study groups were generally well matched with respect to baseline characteristics (*Table 1*). After the optimization period, fewer patients assigned to Ablation and CRT received digoxin ($P = 0.03$) and vasodilators ($P = 0.26$) during the study period than those assigned to the Drug arm; more patients assigned to Ablation and CRT received angiotensin-converting enzyme inhibitors or receptor blocker during the study period than those assigned to the Drug arm ($P = 0.16$). In the Ablation and CRT arm, the median time from randomization to CRT implantation was 2.5 days (interquartile range 1–8). The median time from randomization to AV junction ablation was 6 days (interquartile range 2–21). In four patients, ablation failed to achieve a persistent AV block; they were analysed in the Ablation and CRT arm according to the intention-to treat principle for primary and secondary endpoints and in the Drug arm according to the on-treatment principle for tertiary endpoint. Another three patients, who had a stable AV block after AV junction ablation but underwent only RV pacing, owing to the failure of coronary sinus pacing, were analysed in the Ablation and CRT arm with regard to all endpoints. A defibrillator back-up was given to 22 patients in the Ablation and CRT arm (i.e. a CRT-D device) and to 20 patients in the Drug arm (i.e. an ICD device). During follow-up, a total of 12 patients assigned to the Drug arm, crossed-over to AV junction ablation and CRT after a median of 135 days (interquartile range 58–207).

Outcome

The median duration of follow-up was 16 months, with no significant difference between groups.

On ITT analysis, at the time of study closure, the primary composite outcome of death due to HF, or hospitalization due to HF, or worsening HF had occurred in 10 patients (20%) in the Ablation+CRT arm and in 20 patients (38%) in the Drug arm [HR in the Ablation+CRT arm, 0.38; 95% confidence interval (CI) 0.18–0.81; $P = 0.013$] (*Table 2* and *Take home figure*). No heterogeneity among centres was found: $P = 0.29$. The HR was 0.18 (95% CI 0.05–0.66; $P = 0.010$) in the 43 patients who had an EF ≤35%, and 0.62 (95% CI 0.23–1.70; $P = 0.359$) in the 59 patients who had an EF >35% (Supplementary material online, *Figure S1*). A total of 6 patients (12%) receiving Ablation+CRT and 17 patients (33%) receiving drugs died from any cause or underwent hospitalization for HF (HR 0.28; 95% CI 0.11–0.72; $P = 0.008$). A total of 2 patients (4%) receiving Ablation+CRT and 6 patients (12%) receiving drugs died from any cause (HR 0.30; 95% CI 0.06–1.50; $P = 0.147$). Details of the cause of death are provided in Supplementary material online, *Table S1*. A total of 5 patients (10%) receiving Ablation+CRT and 13 patients (25%) receiving drugs underwent hospitalization for HF (HR 0.30; 95% CI 0.11–0.78); $P = 0.024$). A subgroup analysis of the primary outcome is shown in *Figure 2*. The results of sensitivity analyses of the

primary Endpoint were consistent with the results of the primary analysis (Supplementary material online, *Figure S2*).

Symptoms and physical limitations

Symptoms and physical limitations were assessed by means of on-treatment analysis during the 1 year visit in the 92 patients who attended for follow-up examination. The 50 patients who underwent effective Ablation and CRT had a 36% lower total SSS score than the 42 patients on Drug therapy (10.5 ± 8.7 vs. 16.3 ± 11.2) and a greater reduction from baseline (difference 19.1 ± 10.4 vs. 12.7 ± 11.2); repeated measures ANOVA for treatment effect: $F(1,90) = 8.60$; $P = 0.0043$ (*Table 3*). The EHRA score decreased from the baseline by ≥1 point in 76% of Ablation and CRT patients and in 43% of Drug arm patients, $P = 0.001$. The greatest improvements in symptoms were observed in Ablation and CRT patients with EF >35%, $P = 0.0003$ (*Figure 3*), with a ≥ 1 point reduction in EHRA score in 90% of cases ($P = 0.0003$). At the time of the 1 year visit, the patients in the Ablation and CRT arm had a mean heart rate of 71 ± 5 b.p.m. and a percentage of biventricular pacing of 98% ± 3%; two patients were in sinus rhythm (+ AV block). The Drug arm patients had a mean heart rate of 78 ± 15 b.p.m.; three were in sinus rhythm.

Adverse events

Two patients (1 Ablation and CRT and 1 Drug arm) had appropriate ICD shocks for ventricular tachyarrhythmias after 10 and 5 months, respectively. One patient (Ablation and CRT arm) underwent catheter ablation for recurrent episodes of ventricular tachycardia. Five patients (Drug arm) suffered inappropriate ICD shocks for AF with high ventricular rate. Three patients had lead dislodgement which required repositioning. Two patients (Drug arm) had acute coronary syndrome. In two patients in the Ablation and CRT group and one in the Drug group, a diagnosis of cancer was made after randomization.

Discussion

Compared with pharmacological rate control, AV junction ablation and CRT reduced the risks of death due to HF, or hospitalization due to HF, or worsening HF by 62% and improved specific symptoms of AF by 36% in elderly patients with permanent AF and narrow QRS.

We hypothesizes that the observed benefit was due to the combination of the almost perfect rate regularization achieved by AV junction ablation and CRT pacing, which counteracted the adverse effects of iatrogenic AV block induced by ablation. In the absence of CRT, earlier studies and meta-analyses of AV junction ablation and RV pacing[1–11] were unable to find an improvement in HF, hospitalization and survival in comparison with medical therapy; the improvement in symptoms and quality of life was mostly related to ventricular rate control rather than to improved cardiac function. Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy was the first trial to show an improvement in HF, hospitalization, and survival. Interestingly, while one large controlled study[5] and a meta-analysis of six trials[8] showed a no reduction in mortality from any cause in patients on RV pacing, with a HR of 1.14 (95% CI 0.81–1.6) and 1.18 (0.26–5.22), respectively, a more recent large propensity score-matched controlled study,[12] in which 37% of patients had received biventricular pacing and 63% RV pacing only, showed a

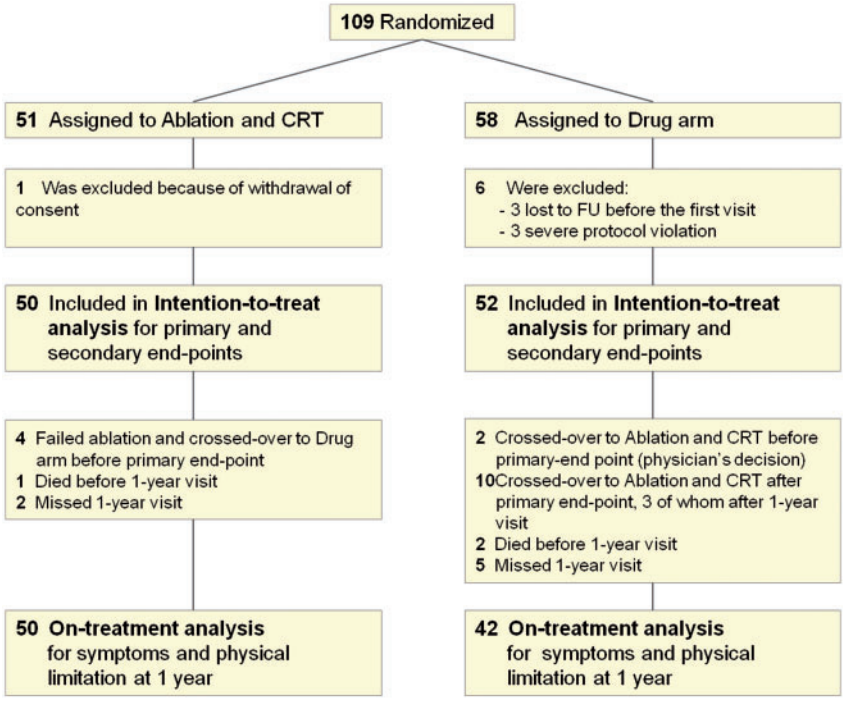


Figure 1 Trial flowchart.

Table 1 Patient characteristics on enrolment

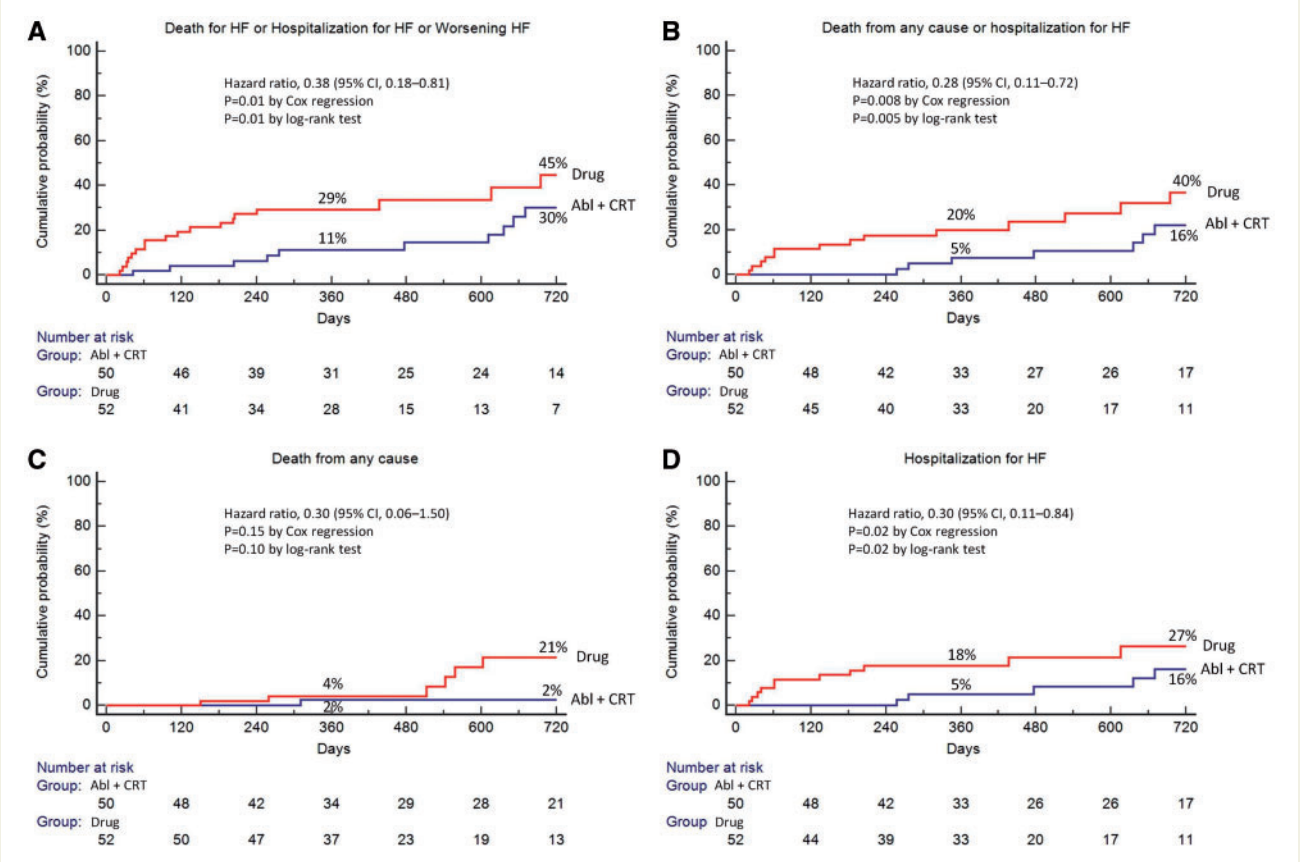
	Abl + CRT ($n = 50$)	Drug ($n = 52$)
Age (years)	71 ± 12	72 ± 9
Male sex	28 (56)	28 (54)
Body mass index	27.5 ± 4.2	29.7 ± 7.7
Systolic blood pressure (mmHg)	124 ± 17	120 ± 14
History of AF		
Duration of permanent AF (months)	13 (8–36)	18 (8–43)
Previous intermittent AF	23 (46)	23 (44)
Duration of intermittent AF (months)	24 (9–53)	18 (12–48)
Previous electrical cardioversion/s	18 (36)	21 (40)
Previous attempt/s at catheter ablation of AF	5 (10)	5 (10)
Number of hospitalizations for HF in the previous year	1.5 ± 0.7	1.7 ± 1.2
Symptoms and physical capacity		
New York Heart Association class ≥III	32 (64)	34 (65)
European Heart Rhythm Association class ≥III	38 (76)	31 (60)
Specific symptoms of atrial fibrillation (SSS) (total score 0–60)	29.2 ± 31.0	29.6 ± 30.5
Palpitations (score 0–10)	4.7 ± 5.0	5.1 ± 3.7
Effort dyspnoea (shortness of breath during physical activity) (score 0–10)	7.4 ± 8.0	8.0 ± 1.7
Rest dyspnoea (shortness of breath at rest), (score 0–10)	3.5 ± 4.0	4.1 ± 3.1
Exercise intolerance (fatigue during mild physical activity) (score 0–10)	7.5 ± 8.0	7.6 ± 2.1
Easy fatigue at rest (score 0–10)	3.8 ± 4.0	3.6 ± 3.0
Chest discomfort (score 0–10)	2.3 ± 2.0	2.1 ± 2.5
Standard electrocardiogram on enrolment		
Heart rate (b.p.m.)	100 ± 23	103 ± 19
QRS width (ms)	97 ± 14	94 ± 12
Echocardiogram		
Left ventricular end-diastolic diameter (mm)	59 ± 12	56 ± 9
Left ventricular end-systolic diameter (mm)	44 ± 10	43 ± 11
Ejection fraction	41 ± 12	40 ± 12
Ejection fraction ≤35%	20 (40)	23 (44)
Medical history		
Hypertension	35 (70)	39 (75)
Diabetes	9 (18)	12 (23)
Coronary heart disease	13 (26)	19 (36)
Dilated cardiomyopathy	12 (24)	7 (13)
Valvular heart disease	11 (22)	7 (13)
Associated mitral valve disease	14 (28)	8 (15)
Stroke/transient ischaemic attack	6 (12)	4 (8)
Pulmonary diseases	8 (16)	9 (17)
Renal insufficiency	10 (20)	9 (17)
Medications (after optimization at 30 days)		
Digoxin	18 (36)*	30 (58)*
Verapamil/diltiazem	6 (12)	6 (12)
Amiodarone/sotalol	1 (2)	3 (6)
Beta-blockers	42 (84)	43 (83)
Diuretics	46 (92)	48 (92)
Angiotensin-converting enzyme inhibitors or receptor blocker	34 (68)	28 (54)
Mineralocorticoid antagonist	25 (50)	27 (52)
Other vasodilators	10 (20)	16 (31)
Antiplatelets	8 (16)	11 (21)
Anticoagulants	47 (94)	48 (92)

Values are given as *n* (%) and continuous variables are given as mean ± SD or median (interquartile range) as appropriate.
*$P = 0.03$.
EF, ejection fraction; HF, heart failure.

Table 2 Hazard ratio for the primary and secondary outcomes (intention-to-treat)

Outcomes	Ablation+CRT ($n = 50$)	Drug ($n = 52$)	Hazard ratio[a] (95% CI)	*P*-value
Combined endpoint of death due to HF, or hospitalization for HF, or worsening HF, pts (%)	10 (20%)	20 (38%)	0.38 (0.18–0.81)	0.013
Combined endpoint and EF ≤35%, pts (%)	3/21 (14%)	11/22 (50%)	0.18 (0.05–0.66)	0.010
Combined endpoint and EF >35%, pts (%)	7/29 (24%)	9/30 (30%)	0.62 (0.23–1.70)	0.359
Combined endpoint of death from any cause, or hospitalization for HF	6 (12%)	17 (33%)	0.28 (0.11–0.72)	0.008
Death from any cause, pts (%)	2 (4%)	6 (12%)	0.30 (0.06–1.50)	0.147
Death due to HF	1	2		
Death due to other causes or unknown	1	4		
Hospitalizations for HF, pts (%)	5 (10%)	13 (25%)	0.30 (0.11–0.84)	0.024
Worsening HF, pts (%)	5 (10%)	8 (15%)	0.55 (0.18–1.68)	0.294

[a]Hazard ratios were calculated by means of the Cox proportional hazard model.
EF, ejection fraction; HF, heart failure; pts, patients.



Take home figure The Kaplan–Meier curves comparing cumulative incidence of the primary and secondary endpoints in the two study groups. (*A*) The cumulative incidence of the primary composite outcome of death due to heart failure, or hospitalization due to heart failure, or worsening heart failure is shown. (*B*) The cumulative incidence of patients who died from heart failure or were hospitalized for heart failure is shown. (*C*) The cumulative incidence of patients who died from any cause is shown. The event rates at one at 2 years of follow-up are shown (*D*) The cumulative incidence of patients who were hospitalized for heart failure is shown..

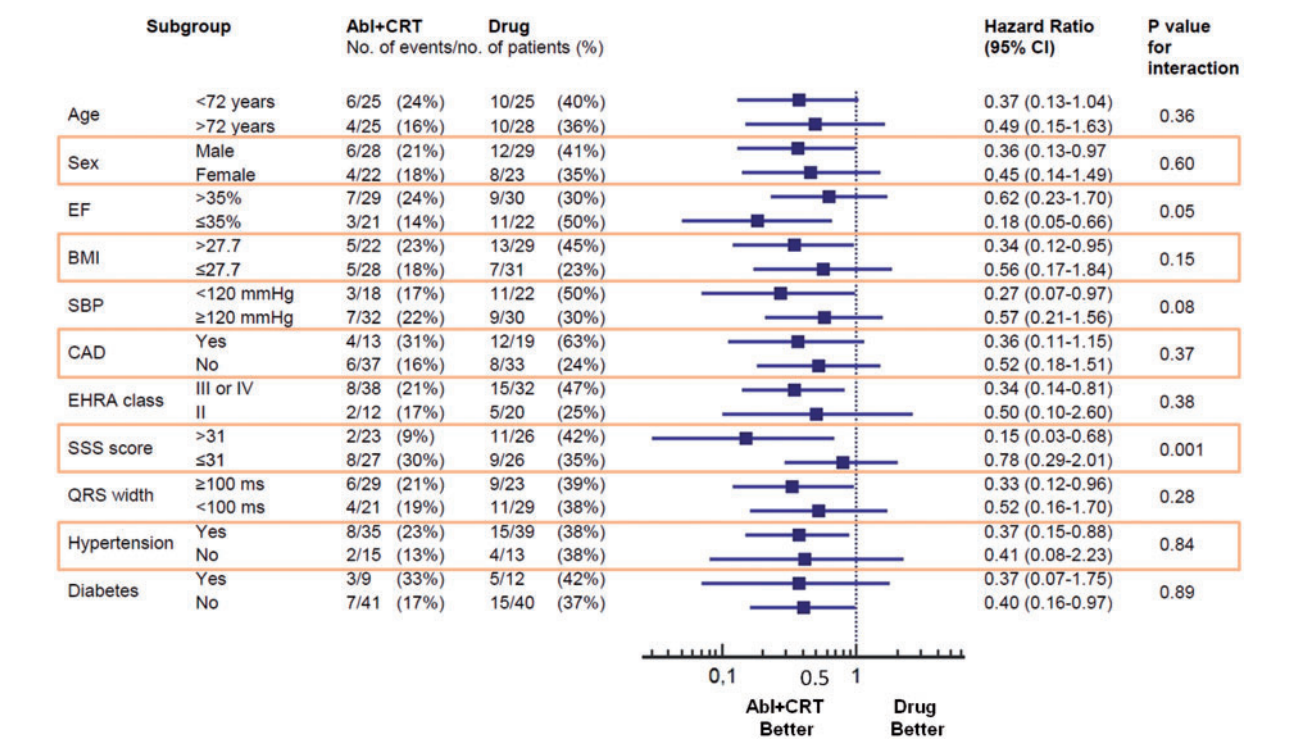


Figure 2 Subgroup analyses of the primary endpoint. Hazard ratio and *P* values for interaction are based on Cox logistic-regression analyses. There was a significant interaction of the primary endpoint (death from heart failure, or hospitalization for heart failure, or worsening heart failure) with ejection fraction and Specific Symptom Scale, which implies that patients with an ejection fraction ≤35% and those with more symptomatic atrial fibrillation (Specific Symptom Scale >31) are more likely to benefit from AV junction ablation and cardiac resynchronization therapy pacing.

Table 3 Quality of life assessed by Specific Symptom Scale score at the baseline and at 1 year follow-up visit (on-treatment analysis) in 50 patients who had effective Ablation + CRT and in 42 patients on Drug therapy

SSS score	Baseline		1 year visit	
	Ablation+CRT	Drug	Ablation+CRT	Drug
SSS score, total (range 1–60)	29.6 ± 9.7	29.0 ± 9.0	10.5 ± 8.7	16.3 ± 11.2
Palpitations (range 1–10)	4.9 ± 3.7	5.3 ± 3.6	1.0 ± 1.4	3.3 ± 3.3
Effort dyspnoea (a) (range 1–10)	7.4 ± 2.0	7.5 ± 2.0	3.2 ± 2.5	4.3 ± 2.4
Rest dyspnoea[a]	3.7 ± 2.8	3.8 ± 2.8	1.2 ± 1.6	1.9 ± 2.1
Effort intolerance[b]	7.4 ± 1.9	7.0 ± 2.4	3.2 ± 2.3	4.3 ± 2.5
Easy fatigue	3.9 ± 3.0	3.2 ± 2.7	1.2 ± 1.6	1.5 ± 1.8
Chest discomfort	2.3 ± 2.6	2.1 ± 2.4	0.8 ± 1.3	1.1 ± 1.9

Values are given as *n* (%) and continuous variables are given as mean ± SD. Repeated measures ANOVA, treatment effect: F(1,90) = 8.60; *P* = 0.0043. The SSS score reduction at the 1 year follow-up visit was greater in the Ablation+CRT group.
[a]Shortness of breath during physical activity.
[b]Fatigue during mild physical activity.

statistically significant reduction [odds ratio= 0.47 (95% CI 0.29–0.77)]. In the present study, in which all patients underwent biventricular pacing, there was a trend toward an even greater reduction in mortality, the HR being 0.30. While these findings suggest a correlation between CRT and mortality reduction, the on-going larger Mortality trial is warranted, in order to confirm this.

APAF-CRT enrolled patients with permanent AF, i.e. according to the ESC guideline definition, 'AF which is accepted by the patient (and physician). Hence, rhythm-control interventions are no longer pursued'.[23] In the other cases, a rhythm-control strategy should be pursued whenever possible.[23] In the PABA-CHF trial,[25] the investigators reported that, on 6 months follow-up examination, AF ablation

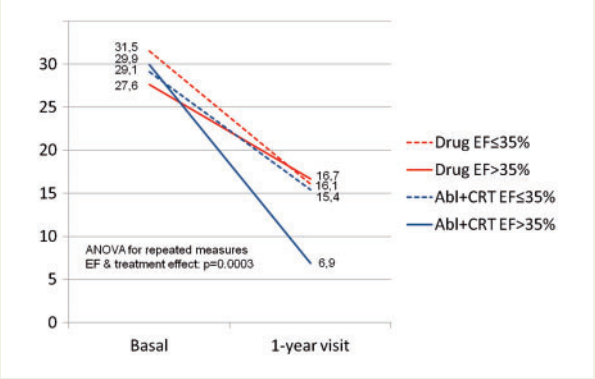


Figure 3 Symptoms and physical limitations assessed by Specific Symptom Scale score, at the baseline and at 1 year follow-up visit. On-treatment analysis in patients with ejection fraction ≤35% and in those with ejection fraction >35%. Mean values and 95% confidence interval are reported. EF, ejection fraction; SSS, specific symptom scale.

was superior to AV junction ablation combined with CRT with regard to the composite Endpoint of EF, 6-min-walk test distance and quality of life. Moreover, in the larger CASTLE trial,[26] the use of ablation for AF in patients with HF was associated with a significantly lower rate of a composite of death from any cause and hospitalization for HF than medical therapy, with a HR of 0.62 (95% CI 0.43–0.87). In that study, however, stable sinus rhythm was difficult to achieve, despite the association of antiarrhythmic drug therapy and repeated procedures in many patients; finally, 40% to 50% of patients failed to maintain sinus rhythm over 60 months of follow-up. The persistence of AF and the harmful effect of antiarrhythmic drug therapy in so many patients in the CASTLE trial might explain why, in APAF-CRT, we achieved an even greater reduction in the combined Endpoint of death from any cause and hospitalization, with a HR of 0.26 (*Table 2* and *Take home figure*). However, the two trials cannot be directly compared, owing to major differences in baseline clinical characteristics. For example, CASTLE patients were, on average, 8 years younger, no patient was older than 71 years, 72% had intermittent AF and 69% were in NYHA Class I or II.

In the APAF-CRT trial, the indication for CRT was primarily an indication for AV junction ablation in order to achieve optimal rate control. Narrow QRS (i.e. <120 ms) is a contraindication for CRT in patients with sinus rhythm.[15–17] Is AV junction ablation a prerequisite for successful CRT even in AF patients with wide QRS who have conventional indications for CRT, as suggested by some registries and meta-analyses?[27–30] In the absence of randomized trials, a substudy of the RAFT trial[31] was unable to show a benefit of CRT without AV junction ablation with regard to the combined Endpoint of death and hospitalization for HF (HR of 0.96). An on-going trial is specifically addressing this issue (RAFT-PermanAF ClinicalTrials.gov Identifier: NCT01994252, last update January 2016).

Limitations

Although the study was terminated in accordance with the prespecified rules, we acknowledge the risk of bias due to termination upon interim analysis and to the small number of events in analysis. Nevertheless, the robustness of the results is reinforced by the positive results of several sensitivity analyses (Supplementary material online). On balance, the morbidity trial should be considered an exploratory trial, the results of which need to be confirmed by the on-going mortality trial.

One of the limitations of the APAF-CRT trial is the lack of blinding with regard to randomization and treatment. Indeed, it would have been quite difficult to perform a truly blinded trial involving a sham ablation procedure. Admittedly, however, this lack of blinding could have led to bias in the adjudication of events, especially with regard to the softer Endpoint of worsening HF. This bias is common to most trials performed on devices or interventions for HF and AF. The effect of this potential bias was, however, mitigated by the fact that the outcomes were adjudicated by an independent blind Clinical Events Committee. Moreover, Drug arm patients with EF <35% also had a device (ICD) implanted, which may have in some way balanced the expectation effect driven by the interventional procedure in the active arm.

Although a greater number of patients in the Drug arm than in the Ablation and CRT arm crossed over to the other treatment group, the results of per-protocol and on-treatment analyses were similar to those of the primary analysis (see Supplementary material online, *Figure S2*).

The definition of permanent AF is highly subjective and is influenced by several factors, including geographical/system differences in the aggressiveness of rhythm-control strategies among centres. This may affect the external validity of the study.

The benefit of ablation plus CRT was higher in patients with low EF. For example, the HR of the composite of death from any cause, or hospitalization from HF, or worsening HF was 0.18 (95% CI 0.05–0.66) in patients with EF ≤35%, 0.45 (95% CI 0.15–1.34) in patients with EF 36–50% and 1.00 (95% CI 0.16–6.00) in patients with EF >50%, thus suggesting no benefit in these latter patients. The Biventricular vs. Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial[32] showed a benefit of CRT over RV pacing in patients with EF ≤50%. Future studies should address the benefit of CRT in patients with normal EF. Ejection fraction value at follow-up would have been useful in correlating the clinical outcome but it was not available being not required by the study protocol.

Finally, this was a selected population of elderly patients recruited from among those referred to a cardiology department, and not from among the total populations of patients hospitalized for HF; our patients might therefore not be fully representative of the general population of patients hospitalized for HF.

Conclusion and perspectives

In conclusion, the results of the APAF-CRT Morbidity trial show that the strategy of AV junction ablation and CRT is both safe and superior to conventional medical strategy in relieving symptoms of HF and reducing hospitalization for HF in elderly patients affected by permanent AF and narrow QRS. Compared with drug therapy, AV junction ablation and CRT yielded an absolute risk reduction of 18% in the composite primary outcome, with a number needed to treat of 5.5; this result was largely driven by the reduction in hospitalizations

for HF. Such interventional therapy should be offered to patients with symptomatic HF refractory to pharmacological therapy who cannot undergo catheter ablation of AF for the maintenance of sinus rhythm, or in whom ablation has failed. While AF-related symptoms are expected to improve more in patients with preserved EF, the reduction in harder endpoints is expected to be more marked in those with reduced EF. Although the Morbidity trial was not sized to assess mortality, the observed trend in reduction in death from any cause justifies the ongoing Mortality trial.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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