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FASTTRACK CLINICAL RESEARCH
Arrhythmias

AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial

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Aims In patients with atrial fibrillation (AF) and heart failure (HF), strict and regular rate control with atrioventricular junction ablation and biventricular pacemaker (Ablation + CRT) has been shown to be superior to pharmacological rate control in reducing HF hospitalizations. However, whether it also improves survival is unknown.

Methods and results In this international, open-label, blinded outcome trial, we randomly assigned patients with severely symptomatic permanent AF >6 months, narrow QRS (≤110 ms) and at least one HF hospitalization in the previous year to Ablation + CRT or to pharmacological rate control. We hypothesized that Ablation + CRT is superior in reducing the primary endpoint of all-cause mortality. A total of 133 patients were randomized. The mean age was 73 ± 10 years, and 62 (47%) were females. The trial was stopped for efficacy at interim analysis after a median of 29 months of follow-up per patient. The primary endpoint occurred in 7 patients (11%) in the Ablation + CRT arm and in 20 patients (29%) in the Drug arm [hazard ratio (HR) 0.26, 95% confidence interval (CI) 0.10–0.65; $P = 0.004$]. The estimated death rates at 2 years were 5% and 21%, respectively; at 4 years, 14% and 41%. The benefit of Ablation + CRT of all-cause mortality was similar in patients with ejection fraction (EF) ≤35% and in those with >35%. The secondary endpoint combining all-cause mortality or HF hospitalization was significantly lower in the Ablation + CRT arm [18 (29%) vs. 36 (51%); HR 0.40, 95% CI 0.22–0.73; $P = 0.002$].

Conclusions Ablation + CRT was superior to pharmacological therapy in reducing mortality in patients with permanent AF and narrow QRS who were hospitalized for HF, irrespective of their baseline EF.

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† A complete list of the investigators in the APAF-CRT trial is provided in the Supplementary material online, *Appendix*.
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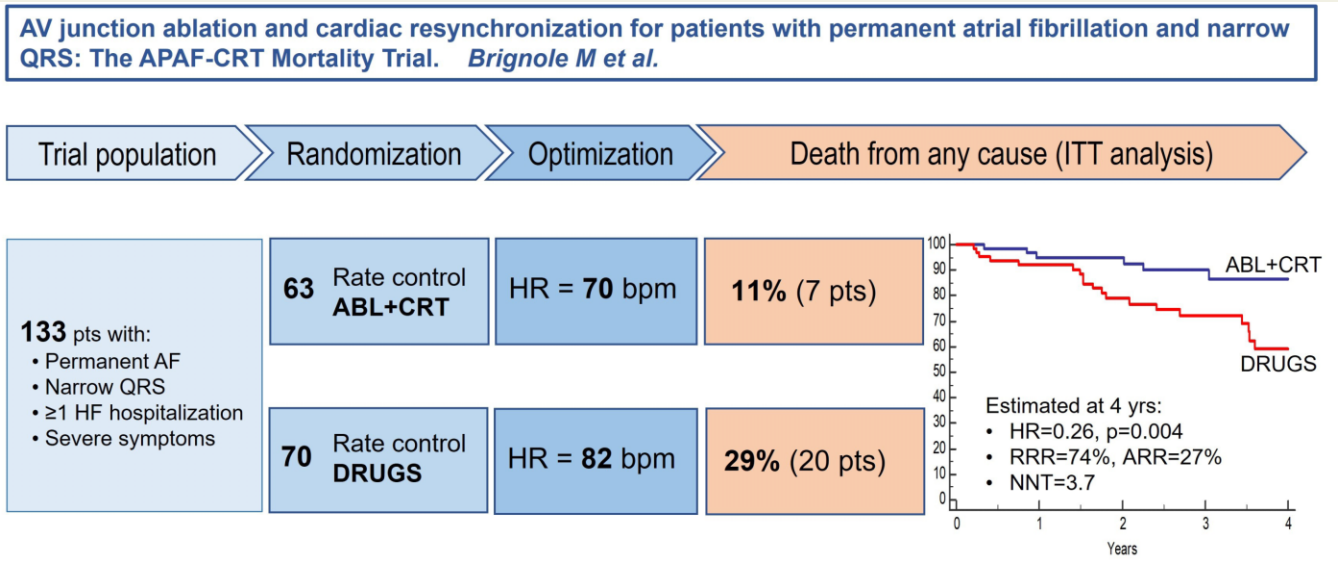
Study registration ClinicalTrials.gov Identifier: NCT02137187.

Graphical Abstract



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

Introduction

Patients with permanent atrial fibrillation (AF) and heart failure (HF) are often treated with pharmacological rate control. Control of the ventricular rate can result in the significant resolution of HF. However, the optimal rate control in patients with AF and HF is unknown. Not only rapid heart rate but also the irregularity contributes to symptoms and possibly to impaired prognosis.[1] Atrioventricular (AV) junction ablation, by slowing and regularizing the ventricular rate, has been shown to improve symptoms, quality of life, and cardiac function, as judged by both physiological and structural measurements. It has been recognized that while rate control is achieved with AV junction ablation, ventricular dyssynchrony caused by permanent right ventricular pacing may adversely affect left ventricular function and interfere with the salutary effects of rate control and rate regularization.[2,3] Biventricular pacing may counteract the adverse effects of non-physiological right ventricular pacing.[4,5] The Ablate and Pace for Atrial Fibrillation—cardiac resynchronization therapy (APAF-CRT) trial involved patients with severely symptomatic permanent AF and narrow QRS and consisted of two consecutive (overlapping) phases, i.e. morbidity trial and mortality trial. The morbidity phase was designed to test the hypothesis that AV junction ablation and biventricular pacing are superior to pharmacological rate control therapy in reducing symptoms of HF and hospitalization for HF.[6]

In the present study, we tested the hypothesis that AV junction ablation and biventricular pacing is superior to pharmacological rate control therapy in reducing all-cause mortality. Figure 1

Methods

Trial design and oversight

APAF-CRT trial was a multicentre, international, prospective, randomized, parallel, open-label, blinded outcome, two-phases trial on patients with severely symptomatic permanent AF and narrow QRS. The morbidity phase showed that AV junction ablation and CRT reduced hospitalization due to HF and improved symptoms of HF compared with pharmacological rate control in elderly patients with permanent AF and narrow QRS at 2 years of follow-up.[6] 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. The authors had unrestricted access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript. APAF-CRT trial is an investigator-initiated independent clinical trial. Data were gathered by the investigators. Electronic management of the data was performed by an

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external company (Airtel, Milan, Italy). Clinical monitoring was performed by an external company (3B Biotech Research, Pavia, Italy). They did not participate in the study design nor in the conduct of the study.

Trial population

Recruitment began in October 2014. As per protocol, recruitment continued after the termination of the morbidity phase and follow-up continued up to 4 years in the APAF-CRT Long-Term Outcome Randomized Clinical Trial (Mortality phase). The mortality phase was conducted in 11 European hospitals from October 2014 till to December 2020. Patients were followed up for a maximum period of 4 years, during which yearly visits were performed. We enrolled patients with the following inclusion criteria: severely symptomatic permanent AF (>6 months), which has been considered unsuitable for AF ablation or in which AF ablation had failed; narrow QRS (≤110 ms); and at least one hospitalization for HF in the previous year. Details regarding exclusion criteria are provided in the Supplementary material online, *Table S4*.

Trial intervention

Patients were randomly assigned in a 1:1 fashion to AV junction ablation and biventricular pacing (plus defibrillator according to guidelines[7]) (Ablation + 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 ejection fraction (EF) (≤35% and >35%).

In the ablation arm, right-sided AV junction ablation was attempted first; the left-sided 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.

Any commercially available CRT-P or CRT-D device was permitted. The right ventricular lead was positioned in the right ventricular apex. The left ventricular lead was targeted to the basal-mid portions of the free wall. No atrial lead was implanted. The final programming of the implanted device was left to the physicians' discretion. Defibrillator backup was chosen at the discretion of the physicians according to ESC guidelines.[7] System reprogramming was recommended during all follow-up visits if persistent capture was not obtained.

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 to achieve a resting heart rate of <110 b.p.m.[8]

Endpoints

The primary endpoint was time to all-cause mortality. Secondary endpoint was time to the composite of all-cause mortality or hospitalization due to HF, whatever came first. Hospitalization for HF was defined as a hospital admission that was associated with an overnight stay owing to the occurrence of increasing symptoms of chronic HF, which necessitated a substantial increase in diuretics and/or appropriate treatment for uncontrolled intolerable AF-related symptoms.

Events were collected by investigators by means of a web-based electronic system and 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.

Statistical analysis

Data analysis

Continuous data are shown as mean ± standard deviation or median (25th–75th percentile), as appropriate. Absolute and relative frequencies were used to compare categorical data. Unpaired Student's *t*-test (or Wilcoxon test in case of no normal data) was used to compare continuous variables, and χ^2 test (or Fisher's exact test) was used to compare proportions. For the analysis of the primary and secondary outcomes, Kaplan–Meier product limit technique was used to build the survival curves of each study groups. Log-rank test was used to test the difference between groups. Moreover, the hazard ratios (HRs) of treatment allocations and their 95% confidence interval (95% CI) were estimated by means of Cox's proportional hazard regression models stratified by centre, after checking for the assumption of hazards' proportionality. Finally, several sensitivity analyses (effect of baseline heart rate, interaction of digoxin, fragility test, and the effect of COVID pandemic) were performed to determine the robustness of the results. All analyses were performed using Statistical Analysis System Software (version 9.4 Institute, Cary, NC, USA).

Sample size justification

In the absence of robust estimation from the literature, we used the results of all-cause mortality observed in the morbidity phase to calculate the sample size of the mortality phase. In the morbidity phase, there were eight all-cause mortality events (two in the Active and six in the Control arm) resulting in a HR of 0.30, 95% CI 0.06–1.50; $P = 0.147$. Based on the HR, with a sequential design, we estimated that with 32 adjudicated primary endpoint events, the mortality phase would have 80% power to detect a reduction in mortality with a two-sided alpha of 0.042.

Interim analysis

According to the sequential study design, the statistical plan was updated to re-calculate the boundaries for study termination at 27 events (i.e. 84% of the statistical information). Using the sequential design boundaries with the Lan–DeMets bounds for a given alpha-spending function, a *P*-value of 0.029 is needed to stop the trial. On 3 February 2021, the Data Safety Monitoring Board informed the sponsor that the difference observed between the two arms fulfilled the stopping rule criterion. In agreement with the Coordinating Clinical Investigator, the sponsor accepted the Board's recommendation to terminate the trial prematurely on account of the evident superiority of the results in one study arm, to minimize risks in the subjects randomized to the control group. Investigators were asked to terminate study procedures with the recommendation to perform AV junction ablation and CRT in the control arm if they deemed it useful according to the present patient's health conditions.

Results

Trial participants

A total of 140 patients were randomized; 133 of these were finally included for analysis and assigned to the Ablation + CRT arm (63 patients) or to the Drug arm (70 patients) (*Figure 2*). The two study groups were generally well matched with respect to baseline characteristics (*Table 1*). After the optimization period, the median heart rate was 70 [interquartile range (IQR) 70–75] b.p.m. in Ablation + CRT group and 82 (IQR 65–90) b.p.m. in the Drug group, $P = 0.03$. The proportion of patients treated with digoxin was similar at enrolment (Supplementary material online, *Tables S3*) but higher in

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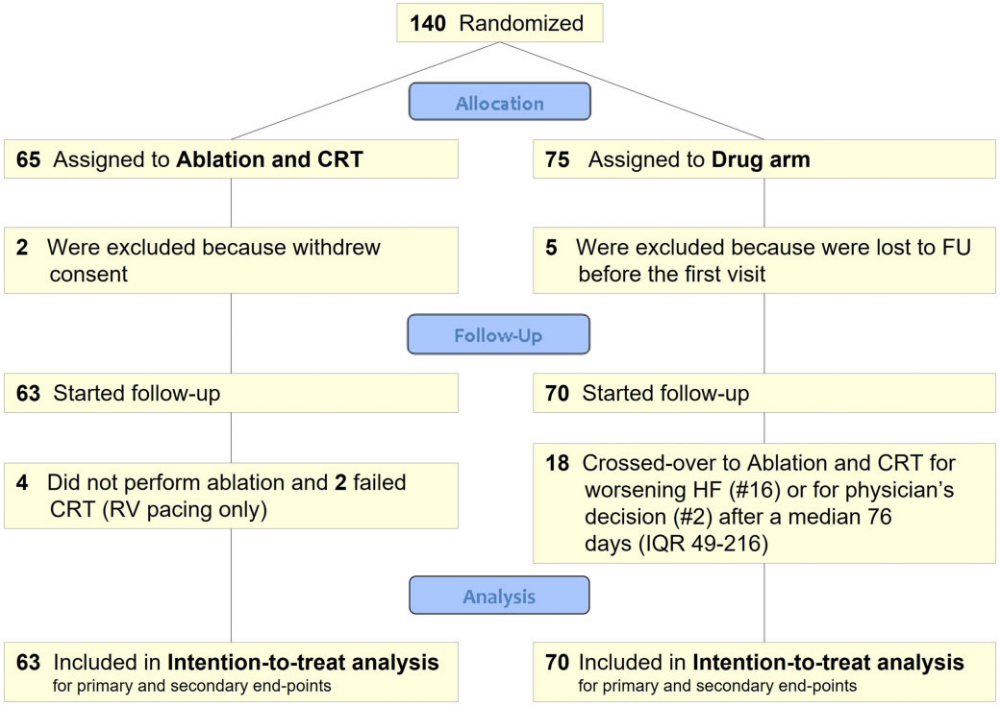

Figure 1 Trial flow chart. CRT, cardiac resynchronization therapy; HF, heart failure; IQR, interquartile range; RV, right ventricular.

the drug group than in the Ablation + CRT group after optimization period, $P = 0.002$.

In the Ablation + CRT arm, the median time from randomization to CRT implantation was 4 days (IQR 1–13) and to AV junction ablation was 6 days (IQR 3–29). A defibrillator back-up was given to 26 patients in the Ablation + CRT arm (i.e. a CRT-D device) and to 20 patients in the Drug arm (i.e. an ICD device), $P = 0.15$; their mean EF was 31% and 32%, respectively.

Eighteen patients in the Drug arm crossed over to the Ablation + CRT arm (*Figure 2*). Of these, 16 crossed over because they had reached the endpoint of HF hospitalization and, as per protocol, they were permitted to perform AV junction ablation and CRT pacing. According to the ITT principle, these patients were analysed in the Drug arm.

Intervention

The median duration of follow-up was 29 (range 1–56) months. The primary endpoint all-cause mortality occurred in 7 patients (11%) in the Ablation + CRT arm and in 20 patients (29%) in the Drug arm (HR 0.26, 95% CI 0.10–0.65; $P = 0.004$) (*Table 2* and *Figure 3A*). The estimated death rates at 2 years were 5% and 21%, respectively, and at 4 years, 14% and 41%.

The secondary endpoint consisting of all-cause mortality or HF hospitalization, whatever came first, was significantly lower in the Ablation + CRT arm [18 (29%) vs. 36 (51%); HR 0.40, 95% CI 0.22–0.73; $P = 0.002$] (*Figure 3B*). The causes of death and hospitalization for HF are listed in the Supplementary material online, *Tables S1 and S2*. In the prespecified subgroup analysis of EF, a benefit in all-cause mortality was observed in patients with EF >35% (HR 0.27, 95% CI 0.08–0.84; $P = 0.024$) with no interaction with patients with EF ≤35% (HR 0.34, 95% CI 0.06–1.92; $P = 0.22$) (*Figure 3C and D*). We assessed the heterogeneity of treatment effects in a *post hoc* analysis, which included age, sex, body mass index, heart rate, specific symptom score, coronary artery disease, and NYHA class as covariates. We found no significant tests for interaction (*Figure 4*). There was also no interaction of heart rate measured at baseline: the survival benefit at 4 years was higher in Ablation + CRT arm compared to both subgroups of Drug arm, those with baseline heart rate ≤102 b.p.m. and those with baseline heart rate >102 b.p.m. Conversely, the survival was similar in the two subgroups of the Drug arm (Supplementary material online, *Figure S1*).

Sensitivity analyses

The interaction of digoxin, the Fragility test and the effect of COVID pandemic are shown in Supplementary material online, *Tables S5–S7*. The results of sensitivity analyses of the primary endpoint were consistent with the results of the primary analysis.

Adverse events

Five patients (4 Ablation + CRT and 1 Drug arm, $P = 0.19$) had appropriate ICD shocks for ventricular tachyarrhythmias. Two patients (Ablation + 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

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Table 1 Characteristics of the patients at baseline

	Ablation + CRT ($n = 63$)	Drug ($n = 70$)
Age (years)	72 ± 11	74 ± 9
Male sex	35 (56)	36 (51)
Body mass index (kg/m^2)	27.6 ± 4.8	28.8 ± 7.4
Systolic blood pressure (mmHg)	123 ± 16	119 ± 15
History of AF		
Duration of permanent AF (months)	19 (8–48)	18 (8–38)
Previous paroxysmal AF	27 (43)	27 (39)
Duration of paroxysmal AF (months)	24 (10–53)	20 (12–48)
Previous electrical cardioversion/s	22 (35)	30 (43)
Previous attempt/s at catheter ablation of AF	5 (8)	8 (11)
Number of hospitalizations for HF in the previous year	1.5 ± 0.8	1.7 ± 1.1
Symptoms and physical capacity		
New York Heart Association Class ≥III	42 (67)	49 (70)
Specific symptoms of AF (total score 0–60)	28.3 ± 10.2	30.1 ± 9.2
Palpitations (score 0–10)	4.7 ± 3.6	4.8 ± 3.7
Effort dyspnoea (shortness of breath during physical activity) (score 0–10)	7.3 ± 2.4	8.0 ± 1.7
Rest dyspnoea (shortness of breath at rest) (score 0–10)	3.6 ± 2.8	4.0 ± 3.1
Exercise intolerance (fatigue during mild physical activity) (score 0–10)	7.1 ± 2.2	7.6 ± 2.1
Easy fatigue at rest (score 0–10)	3.6 ± 2.9	3.8 ± 3.0
Chest discomfort (score 0–10)	2.1 ± 2.7	2.0 ± 2.4
Standard electrocardiogram on enrolment		
Heart rate (at enrolment) (b.p.m.)	101 ± 22	103 ± 19
Heart rate (after optimization at 30 days) (b.p.m.)	70 (70–75)	82 (65–90)*
QRS width (ms)	95 ± 12	94 ± 12
Echocardiogram		
Ejection fraction	41 ± 12	41 ± 12
Ejection fraction ≤35%	27 (43)	28 (40)
Median	30 (25–31)	30 (26–34)
Ejection fraction >35%	36 (57)	42 (60)
Median	50 (45–55)	49 (40–51)
Medical history		
Hypertension	46 (73)	52 (74)
Diabetes	14 (22)	18 (26)
Coronary heart disease	16 (25)	25 (36)
Dilated cardiomyopathy	13 (21)	9 (13)
Primary valvular heart disease	13 (21)	11 (16)
Secondary mitral valve disease	17 (27)	13 (19)
Stroke/transient ischaemic attack	6 (10)	5 (7)
Pulmonary diseases	15 (24)	13 (19)
Renal insufficiency	13 (21)	18 (26)
Medications (after optimization at 30 days)		
Digoxin	20 (32)	42 (60)**
Verapamil/diltiazem	8 (13)	8 (11)
Amiodarone/sotalol	1 (2)	7 (10)
Beta-blockers	51 (81)	61 (87)
Diuretics	58 (92)	66 (94)
Angiotensin-converting enzyme inhibitors or receptor blocker	41 (65)	38 (54)
Mineralocorticoid antagonist	29 (46)	33 (47)
Other vasodilators	14 (22)	14 (20)
Antiplatelets	10 (16)	13 (19)
Anticoagulants	60 (95)	64 (91)

Values are *n* (%) and continuous variables are given as mean ± SD or median (interquartile range) as appropriate.
AF, atrial fibrillation; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; SD, standard deviation.
*$P = 0.03$.
**$P = <0.001$.

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Table 2 Efficacy outcomes[a]

Outcomes	Ablation + CRT ($n = 63$)	Drug ($n = 70$)	Hazard ratio[b] (95% CI)	*P*-value
Death from any cause (patients)	7 (11%)	20 (29%)	0.26 (0.10–0.65)	0.004
Cardiovascular cause	5 (8%)	12 (17%)	0.35 (0.12–1.02)	0.05
Non-cardiovascular cause	2 (3%)	8 (11%)	0.25 (0.05–1.16)	0.08
Combined endpoint of death from any cause or hospitalization for HF, patients (%)	18 (29%)	36 (51%)	0.40 (0.22–0.73)	0.002
Death from any cause and EF ≤35% (patients)	3/27 (11%)	8/26 (31%)	0.34 (0.06–1.92)	0.22
Death from any cause and EF >35% (patients)	4/36 (11%)	12/44 (27%)	0.27 (0.08–0.84)	0.02

CI, confidence interval; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure.
[a]The primary and secondary clinical outcomes were analysed according to the intention-to-treat principle.
[b]Hazard ratios were calculated by means of the Cox proportional hazard model.

patients had lead dislodgement (two coronary sinus and one right apical lead position), which required repositioning. One patient had repeated AV junction procedure after 20 days because of AV block regression.

Discussion

In this investigator-initiated, multicentre randomized trial, a strategy of AV junction ablation and CRT in patients with permanent AF, narrow QRS and at least one hospitalization reduced the risk of death from any cause during a follow-up of 4 years. The survival curves progressively diverged with the length of observation. At 4 years, the relative and absolute risk reductions were 74% and 27%, respectively, and the number needed to treat was 3.7. Moreover, AV junction Ablation and CRT reduced the combined risks of death from any cause or hospitalization for HF by 60%. The benefit during the initial years of observation was mostly attributable to fewer hospitalizations and that during the late years was g mostly attributable to fewer deaths. Finally, a benefit in all-cause mortality was observed in patients with preserved EF with no interaction between patients with EF >35% and those ≤35%. We hypothesize that the observed benefit was due to the combination of the strict rate control and rate regularization achieved by AV junction ablation together with biventricular pacing, which counteracted the adverse effects of right ventricular pacing.[4,5]

APAF-CRT shows an improvement in survival in patients with permanent AF and narrow QRS. Interestingly, while one large, controlled study[9] and a meta-analysis of six trials[10] showed no reduction in mortality from any cause in patients after AV junction ablation and right ventricular pacing, a recent large propensity-score-matched controlled study,[11] in which 37% of patients had received biventricular pacing and 63% right ventricular pacing only showed a statistically significant reduction (odds ratio = 0.47). Thus, when the confounding effect of non-physiological right ventricular pacing is overcome by CRT,[4,5] the almost optimal rate regularization achieved with AV junction ablation emerges as the main determinant of improved cardiac function, reduction in mortality, and hospitalization. This conclusion is supported by old robust physiology studies.[12–14] The strict rate control with reduction in the ventricular rate from ∼100 b.p.m. before ablation to 70 b.p.m. after ablation is likely to have contributed to the observed benefit. Indeed, contrary to RACE II trial,[8] which was unable to show a benefit of strict rate vs. lenient rate control, the APAF-CRT patients had more severe HF, a perfect rate regularization and less adverse effects of rate-controlling drugs. In the absence of rate regularization provided by AV junction ablation, CRT alone was ineffective in the AF substudy of the RAFT trial,[15] in a multicentre observational study[16] and in a meta-analysis.[17] Furthermore, CRT was ineffective in patients in sinus rhythm and QRS <120 ms.[18]

APAF-CRT like patients is a population of highly symptomatic permanent AF patients who had had at least one hospitalization for HF. The mortality rate observed in the control group was ∼40% at 4 years. This high mortality rate is similar to that observed in a Swedish nation-wide long-term case–control study[19] in patients hospitalized for AF. This latter study had also similar age, similar gender distribution, and similar rate of concomitant diseases.

Digoxin was prescribed more often in the control group, but sensitivity analysis showed consistent results with the primary analyses. Meta-analyses and retrospective analyses showed that digoxin in patients with AF is associated with an increased mortality.[20,21] Neutral effects were, however, also reported.[22] A meta-analysis showed no effect in patients with AF and HF but did in patients without AF and HF.[23]

Contrary to patients in sinus rhythm, in whom CRT has been shown to be clinically useful mainly for patients with HF with EF ≤35%, the AF population is heterogeneous with various underlying risk factors and pathophysiological abnormalities, where atrial cardiomyopathy probably plays a major role.[24] In the present study, most patients had an EF of >35%. A benefit in all-cause mortality was observed in patients with preserved EF with no interaction between patients with EF >35% and those with EF ≤35%. This finding suggests a minor prognostic role of the classical parameter of EF and conversely emphasizes the major role of rate irregularity in causing HF.

The results of the present study cannot be extended to the patients with AF and wide QRS who have conventional indications for CRT. However, a survival benefit was observed in wide QRS patients in a multicentre observational study[16] and in a systematic review and meta-analysis.[17]

The results of the present trial cannot be directly compared with those of AF ablation trials, owing to different major differences in inclusion criteria and clinical characteristics. For example, CASTLE

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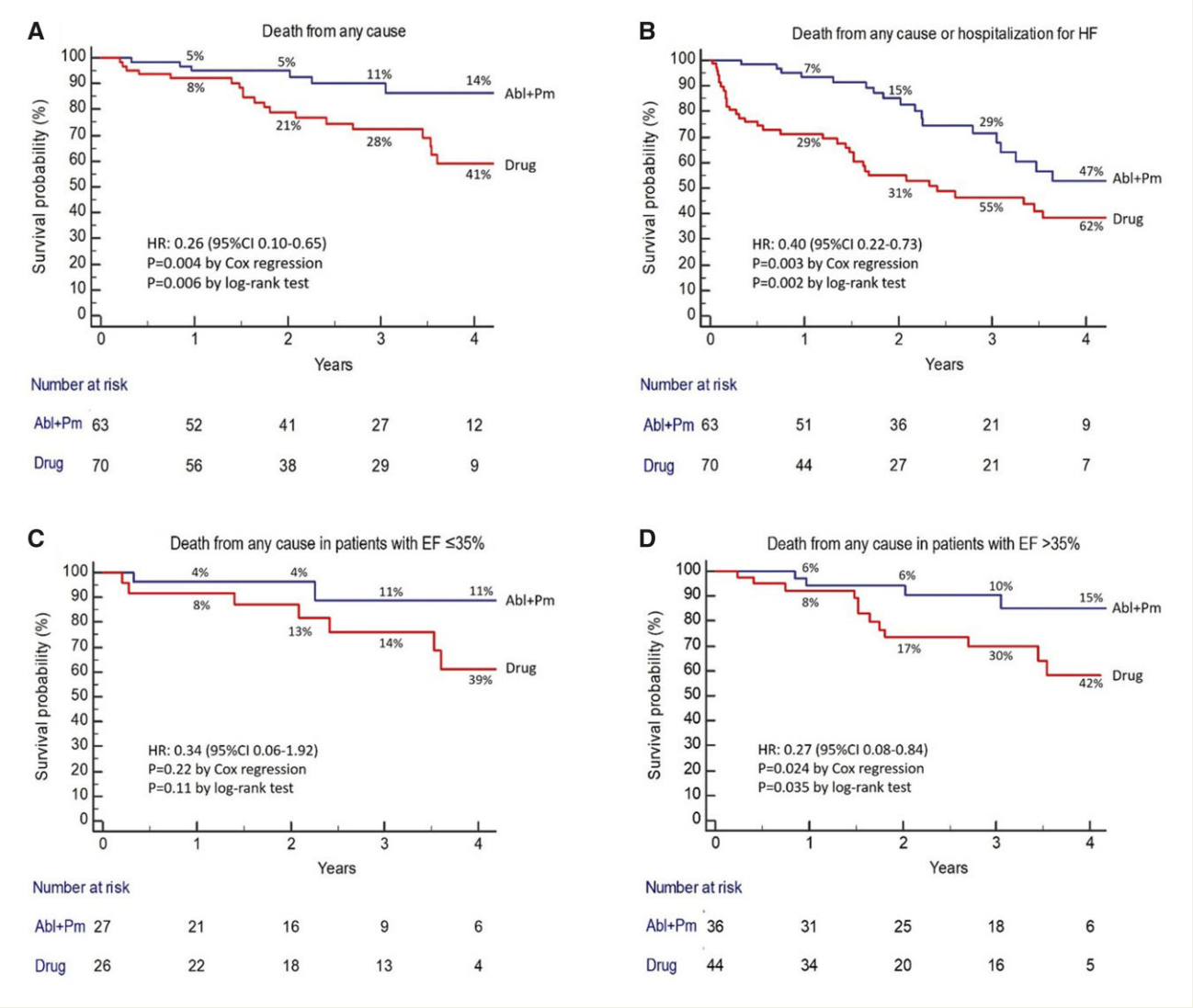

Figure 2 Kaplan–Meier curves comparing primary and secondary outcomes between Ablation + Cardiac Resynchronization Therapy arm and Drug arm. Event-free probability and yearly cumulative incidence are shown. (*A*) The incidence of the primary outcome of death from any cause. (*B*) The incidence of combined endpoint of death from any cause or hospitalization for heart failure. (*C*) The incidence of death from any cause in patients with ejection fraction ≤35%. (*D*) The incidence of death from any cause in patients with ejection fraction >35%. CI, confidence interval; EF, ejection fraction; HF, heart failure; HR, hazard ratio.

trial[25] patients were, on average, 8 years younger and no patient was older than 71 years. The mortality rates in the CASTLE trial were 13.4% in ablation group vs. 25.0% in the drug group (HR 0.53). Among the AF patients who had clinically diagnosed stable HF at trial entry (mostly with preserved EF), enrolled in a sub study of CABANA trial,[26] the ablation arm had a 43% relative reduction in all-cause mortality (HR 0.57; 95% CI 0.33–0.96) compared to drug therapy alone over a median follow-up of 48.5 months.

Some limitations should be noted. The relatively small population of the trial could question the generalizability of the results. Most patients had advancing age and had New York Heart Association Class ≥III. The characteristics of the APAF-CRT patients resemble that of the general population of highly symptomatic elderly AF patients who had had at least one hospitalization for HF.[19] Thus, generalizability to less severe HF is limited. Adequacy of rate control in the Drug arm deserves some comments. The study protocol did not include procedures for the assessment of medical rate control. Optimization of pharmacological therapy was left to investigator's decision according to their clinical practice. In theory, a more adequate strict rate control (e.g. by increasing beta-blocker dosage) could be protective and equivalent to ablate and pace. Several reasons make this hypothesis unlikely: (i) there was no interaction of heart rate measured at baseline and, in the Drug arm, the survival benefit was similar in patients with baseline heart rate ≤102 b.p.m. and those with baseline heart rate >102 b.p.m (Supplementary material online, *Figure S1*); (ii) RACE II trial[8] was unable to show a benefit of strict rate vs. lenient rate control; and (iii) in a meta-analysis of randomized trials,[27] beta-blockers were unable to show a benefit in survival in patients

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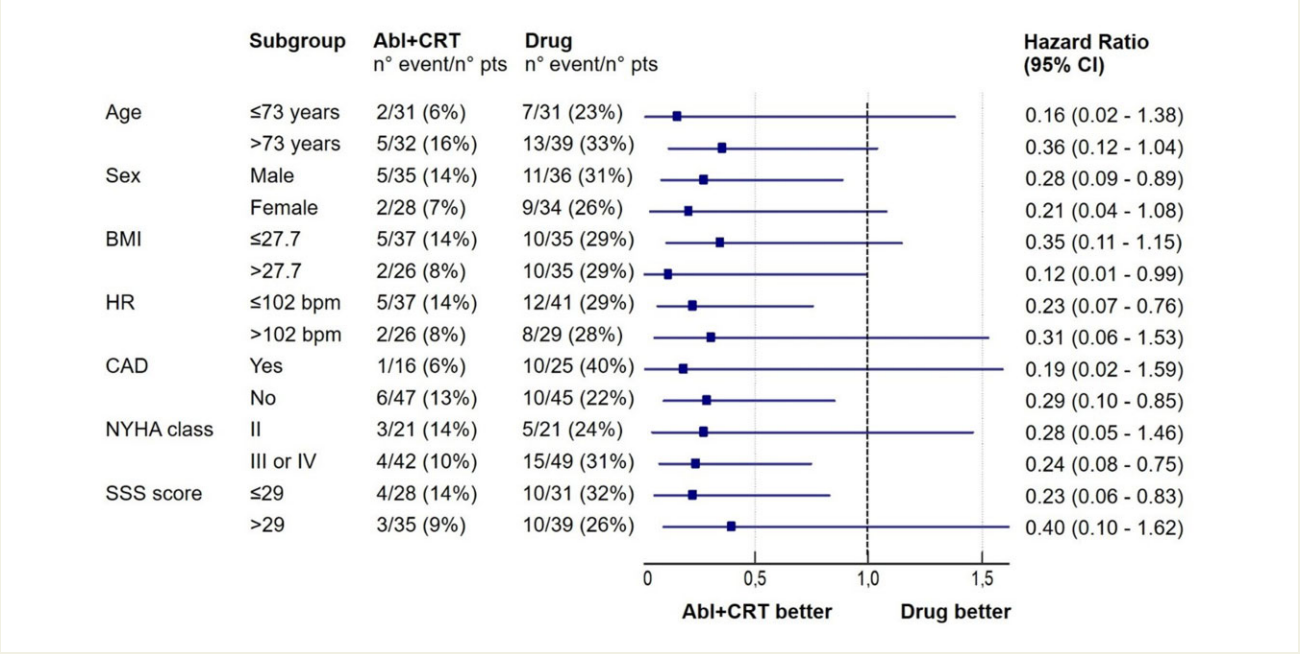

Figure 3 Subgroup analyses of the primary endpoint. A subgroup analysis of the primary outcome did not evidence interactions between subgroups. BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CRT, cardiac resynchronization therapy; HR, heart rate; NYHA, New York heart Association class; SSS, Specific Symptoms Scale score.

with AF, which was irrespective of heart rate, HR = 0.97. COVID-19 pandemic had an impact on the running of the trial. The effect of COVID-19 on results was assessed in sensitivity analysis, which showed that the results of the primary endpoint were consistent with the results of the primary analysis. Five percent of randomized patients were lost to follow-up and could not be analysed. Finally, future randomized controlled trials comparing biventricular pacing with conduction system pacing are warranted.

In conclusion, the improvement in survival showed by APAF-CRT trial supports ablation plus CRT as a first-line therapy in patients with permanent AF and narrow QRS who were hospitalized for HF, irrespective of their baseline EF.

Supplementary material

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

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Data availability

Data are available upon reasonable request to Michele Brignole at mbrignole@outlook.it.

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