Supplementary Data

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Brignole M, Pentimalli F, Palmisano P, et al. “AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: The APAF-CRT Mortality Trial”

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The task of the CEAC was to adjudicate cause of death and reason for hospitalization. Roles and responsibilities of the CEAC are detailed in the study protocol, pages 14-16. According to the DSMB charter, an independent DSMB has been convened to assess the progress of the investigation study, the safety data, the critical efficacy endpoints and provide recommendations to the sponsor. The members of the DSMB serve in an individual capacity and provide their expertise, including recommendations regarding the continuation, modification, or termination of the study.

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Sponsor and Funding

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Additional results

Table S1 - Causes for death

Twenty-seven patients died during the study period, 7 of them had been randomized to Ablation + CRT arm and 20 to Drug arm.

Pt no.	Group	ADC decision	Description
1	Abl + CRT	CV-HF	Was hospitalized for end-stage HF which was refractory to diuretic increase and inotropic therapy.
2	Abl + CRT	CV-HF	Hospitalized for recurrence of HF
3	Abl + CRT	CV-SCD	Died in the periprocedural period of a surgical intervention for prostatic disease; had pulseless electrical activity at the time of death
4	Abl + CRT	CV-SCD	Unexpected SCD while in institutionalized nursing home
5	Abl + CRT	CV-Others	Hospitalized for stroke, died after 7 days
6	Abl + CRT	Non-CV	Subdural hematoma in patients with pulmonary cancer
7	Abl + CRT	Non-CV	Sepsis complicated by renal insufficiency
8	Drug	CV-HF	Died in-hospital for end-stage HF complicated by renal insufficiency
9	Drug	CV-HF	Died at home for end-stage HF
10	Drug	CV-HF	Died at home for end-stage HF
11	Drug	CV-HF	Died at home for low-output HF
12	Drug	CV-HF	Died at home for low-output HF
13	Drug	CV-HF	Died at home for HF
14	Drug	CV-SCD	SCD during night
15	Drug	CV-Others	Died in hospital for acute intestinal infarction
16	Drug	CV-Others	Died in hospital for acute pulmonary embolism
17	Drug	CV-Others	Died in hospital for acute renal insufficiency, multiorgan disease and possible pulmonary embolism
18	Drug	CV-Others	Died in hospital for ischemic stroke
19	Drug	CV-Others	Died while hospitalized for rehabilitation of previous ischemic stroke
20	Drug	Non-CV	Died in hospital for bronchopneumonia
21	Drug	Non-CV	Died in hospital for bronchopneumonia
22	Drug	Non-CV	Died at home for terminal bladder cancer
23	Drug	Non-CV	Leukemia
24	Drug	Non-CV	Acute myeloblastic leukemia
25	Drug	Non-CV	Had cognitive deterioration, difficulty in ambulation, no HF
26	Drug	Unknown	Unspecified respiratory failure
27	Drug	Unknown	Reported by census

ADC means Adjudication Committee; Abl+CRT means ablation and CRT group; CV means cardiovascular; HF means heart failure; SCD means sudden cardiac death.

Hospitalizations

Overall, there were 62 hospitalizations in 40 patients during the follow-up. Of these, 47 were for HF, 9 for other cardiovascular reasons not related to HF and 6 for non-cardiac diseases.

Thirty-eight patients were hospitalized for HF and were discharged alive during the study period, 13 of them had been randomized to Ablation + CRT arm and 25 to Drug arm.

Table S2 – Hospitalization for HF

Pt no.	Group	ADC decision	Description
1	Abl + CRT	CV-HF	2 admissions for acute HF
2	Abl + CRT	CV-HF	1 admissions for HF
3	Abl + CRT	CV-HF	2 admissions for HF
4	Abl + CRT	CV-HF	2 admissions for HF
5	Abl + CRT	CV-HF	1 admissions for HF after withdrawal of diuretic therapy (patient's decision)
6	Abl + CRT	CV-HF	1 admissions for HF
7	Abl + CRT	CV-HF	1 admission for acute HF
8	Abl + CRT	CV-HF	1 admission for chronic HF, cognitive deterioration, renal insufficiency
9	Abl + CRT	CV-HF	1 admission for congestive HF and pleural effusion
10	Abl + CRT	CV-HF	1 admissions for HF, chronic renal insufficiency and anemia
11	Abl + CRT	CV-HF	3 admissions for HF
12	Abl + CRT	CV-HF	1 admission for congestive HF
13	Abl + CRT	CV-HF	1 admission for congestive HF
14	Drug	CV-HF	1 admission for congestive HF and ICD shocks
15	Drug	CV-HF	2 admissions for HF; the second one led to cross-over to Abl+Pm, then improvement of symptoms
16	Drug	CV-HF	1 admission for acute pulmonary edema
17	Drug	CV-HF	1 admission for HF due to tachycardiomyopathy that led to Abl+Pm, then 2 other admissions for congestive HF
18	Drug	CV-HF	1 admission for HF
19	Drug	CV-HF	1 admission for HF that led to cross-over to Abl+Pm, then asymptomatic
20	Drug	CV-HF	1 admission for congestive HF
21	Drug	CV-HF	1 admission for HF due to tachycardiomyopathy
22	Drug	CV-HF	1 admission for HF that led to cross-over to Abl+Pm; died for HF after 41 months
23	Drug	CV-HF	1 admission for HF that led to cross-over to Abl+Pm, then asymptomatic
24	Drug	CV-HF	1 admission for HF that led to cross-over to Abl+Pm, then asymptomatic
25	Drug	CV-HF	1 admission for HF due to severe mitral insufficiency that led to transcutaneous repair with mitraclip
26	Drug	CV-HF	1 admission for HF
27	Drug	CV-HF	1 admission for HF
28	Drug	CV-HF	1 admission for HF that led to cross-over to Abl+Pm, then asymptomatic
29	Drug	CV-HF	2 admissions for HF; the second one led to cross-over to Abl+Pm, then asymptomatic
30	Drug	CV-HF	1 admission for HF and acute coronary syndrome
31	Drug	CV-HF	2 admissions for congestive HF; died one month after the second admission
32	Drug	CV-HF	2 admissions for HF; the second one led to cross-over to Abl+Pm, then asymptomatic
33	Drug	CV-HF	1 admission for HF due to tachycardiomyopathy; cross-over to Abl+Pm, then asymptomatic
34	Drug	CV-HF	1 admission for congestive HF that led to cross-over to Abl+Pm, then asymptomatic
35	Drug	CV-HF	1 admission for congestive HF that led to cross-over to Abl+Pm, then asymptomatic
36	Drug	CV-HF	1 admission for HF due to tachycardiomyopathy
37	Drug	CV-HF	1 admission for congestive HF
38	Drug	CV-HF	1 admission for HF that led to cross-over to Abl+Pm, then asymptomatic

ADC means Adjudication Committee; CV means cardiovascular; HF means heart failure

Table S3. Medications at enrolment

	Abl + CRT (n=63)	Drug (n=70)
- Digoxin	34 (54)	26 (37)
- Diuretics	56 (89)	65 (93)
- Beta-blockers	51 (81)	59 (84)
- Verapamil/diltiazen	11 (17)	7 (10)
- Amiodarone	2 (3)	10 (14)
- Angiotensin converting enzyme inhibitors or receptor blocker	38 (60)	38 (54)
- Mineralocorticoid antagonist	32 (51)	36 (51)
- Nitrates	3 (5)	5 (7)
- Alpha-antagonists	8 (13)	7 (10)
- Dyhydropyridinic calcium antagonists	4 (6)	5 (7)
- Antiplatelets	9 (14)	14 (20)
- Anticoagulants	62 (98)	65 (93)

Values are n (%) and continuous variables are given as mean ± SD or median (interquartile range) as appropriate

Table S4. Exclusion criteria

Patients were excluded if as follows:

1) hospital NYHA class IV and systolic blood pressure ≤80 mmHg despite optimized therapy;

2) severe concomitant non-cardiac disease;

3) need for surgical intervention;

4) myocardial infarction within the previous 3 months;

5) previously implanted devices (pacemaker/ICD/CRT) with ≥5% pacing function. Patients who had devices implanted that had <5% of paced beats (i.e., back-up pacing) could be enrolled.

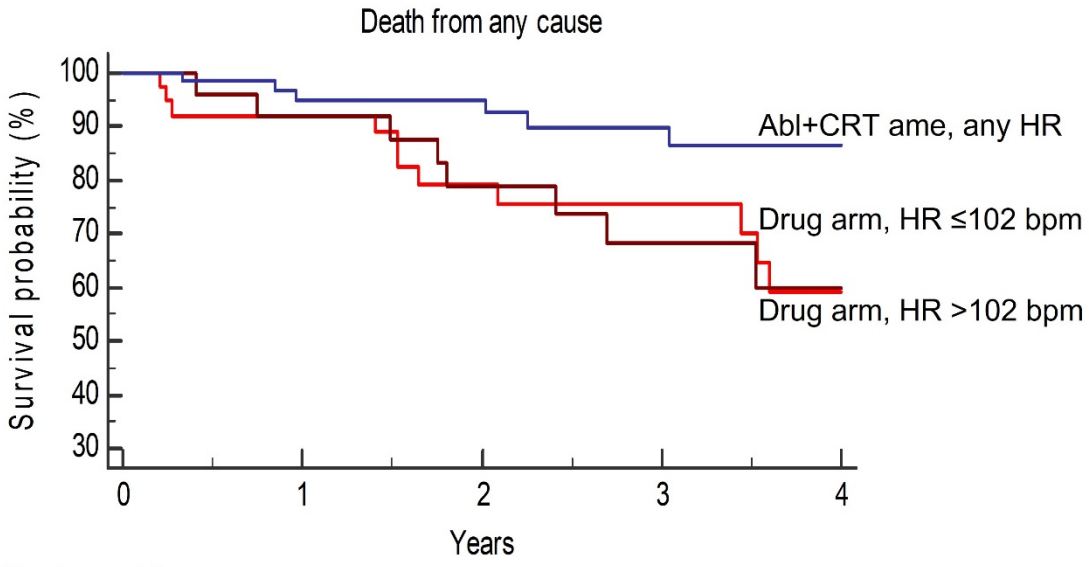
Sensitivity analysis

The sensitivity analyses covered the following aspects:

- Effect of baseline heart rate (Figure S1)
- Interaction of digoxin after optimization (Table S5)
- Fragility test and effect of COVID 19 pandemic (Tables S6 and S7)

Figure S1. Effect of baseline heart rate

The survival benefit at 4 years was higher in Ablation+CRT arm compared to both subgroups of Drug arm, those with baseline HR ≤102 and those with HR >102: 14% versus 41% and 41% respectively:
Ablation+CRT versus Drug HR ≤102: HR=0.31 (96% CI 0.11-0.87)
Ablation+CRT versus Drug HR >102: HR=0.32 (96% CI 0.13-0.77)
A similar survival at 4 years was observed in the Drug arm patients with baseline HR ≤102 with those with HR >102: HR=0.96 (96% CI 0.42-2.56)



Number at risk

Drug ≤102	41	33	22	17	5
Drug >102	29	23	16	12	4
Abl+CRT	63	52	41	27	12

Interaction of digoxin after optimization

After optimization, the proportion of patients treated with digoxin was higher in the drug group than in the Ablation and CRT group (p=0.002). The following table analyses the interaction of digoxin with the outcome.

Table S5. Interaction of digoxin after optimization

Predictor	Model	Hazard ratio	95% CI	P value
Abl + Pm versus Drug	Cox proportional regression	0.24	0.10 – 0.60	0.02
Digoxin		0.44	0.20 – 0.97	0.04

Fragility test and effect of COVID 19 pandemia

The ”Fragility” of the primary end-point result was assessed by iterative estimates of the Hazard Ratio (HR) and significance for incremental events from 5 to 27 (the observed events during the trial)(Figure S5). For this analysis, the follow-up of all sample was stopped at the date of death of the relative event. From the 8th event onwards, the estimated HR is statistically significant ($p < 0.05$) and its value sufficiently stabilizes after the 13th event.

Table S6. Fragility test

Events	Arm	Year of death	HR*	p
1	Drug	2016		
2	Drug	2016		
3	ABL+Pm	2016		
4	Drug	2016		
5	Drug	2016	0.23	0.19
6	Drug	2017	0.20	0.14
7	Drug	2017	0.15	0.08
8	Drug	2017	0.12	0.05
9	Drug	2017	0.11	0.04
10	Drug	2017	0.10	0.03
11	ABL+Pm	2018	0.19	0.04
12	Drug	2018	0.18	0.02
13	ABL+Pm	2018	0.26	0.04
14	Drug	2018	0.25	0.03
15	Drug	2019	0.23	0.02
16	ABL+Pm	2019	0.31	0.04
17	Drug	2019	0.29	0.03
18	Drug	2019	0.27	0.02
19	Drug	2019	0.26	0.02
20	Drug	2019	0.24	0.01
21	ABL+Pm	2019	0.22	0.006
22	Drug	2019	0.22	0.006
23	Drug	2019	0.21	0.005
24	Drug	2019	0.20	0.004
25	Drug	2019	0.19	0.002
26	ABL+Pm	2020	0.22	0.003
27	ABL+Pm	2020	0.26	0.004

*estimated by univariate Cox's proportional hazard model.

Pre-COVID-19 sensitivity analysis on the primary and secondary outcomes.

The management and follow-up of patients was affected by the COVID-19 pandemic. The impact of COVID-19 cases, related changes in health-care services provided, and the potential consequences of COVID-19 on heart failure epidemiology [1,2] have been acknowledged as a serious and unpredictable threat to the conduct of clinical trials.[3,4,5] Based on recommendations by the Heart Failure Association of the European

Society of Cardiology [3] and the European Medicines Agency [4] and the US Food and Drug Administration,[6] the statistical analysis plan included a pre-COVID-19 sensitivity analysis, censoring patients in each country at the date when its first COVID-19 patient was reported. The analyses were prespecified in the statistical analysis plan before locking the database. The pre-COVID-19 sensitivity analysis showed a significant benefit of Ablation+CRT on all-cause mortality and hospitalization (Table S6). At the initial outbreak of the COVID-19 pandemic in February 2020, patient follow-up was continuing. Both patient safety and the potential impact of COVID-19 on the data integrity and completeness of follow-up was discussed and several mitigation plans were implemented. For example, patients could be contacted by telephone for the planned study visits instead of returning to the outpatient clinic visit planned by the study protocol. The number of heart failure hospitalisations was reportedly reduced in Europe. We are unable to predict what influence COVID-19 might have had on a treatment effect, but it is plausible that less complete follow-up, fewer hospitalisations, and a general lack of protocol compliance could have diluted the ability to observe treatment differences[7]. Thus, we consider our prespecified COVID-19 sensitivity a judicious analysis.

Table S7. Hazard Ratio for the primary and secondary outcomes (intention-to-treat)

Outcomes	Ablation + CRT	Drug	Hazard Ratio* (95% CI)	p value
Death from any cause, pts (%):	7/63 (11)	20 /70 (29)	0.26 (0.10-0.65)	0.004
-cardiovascular cause	5 (8)	12 (17)		
-non-cardiovascular cause	2 (3)	8 (11)		
Combined endpoint of death from any cause or hospitalization for HF, pts (%)	18/63 (29)	36/70 (51)	0.40 (0.22-0.73)	0.002
Pre-COVID-19 sensitivity analysis				
Death from any cause, pts (%):	5/60 (8)	20/63 (32)	0.17 (0.06-0.51)	0.002
-cardiovascular cause	5	12		
-non-cardiovascular cause	0	8		
Combined endpoint of death from any cause or hospitalization for HF, pts (%)	14/60 (23)	32/63 (51)	0.24 (0.11-0.52)	0.0004

* Hazard ratios were calculated by means of the Cox proportional-hazard model.
EF means ejection fraction, HF means heart failure

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