

Effects of Ablation Versus Drug Therapy on Clinical Outcomes and Quality of Life by Frailty Status in Atrial Fibrillation: A Posthoc Analysis of the CABANA Trial

Brief Title: Frailty Influences Treatments in AF

Lili Wang ^{1#}, Yanguang Li ¹, Qiaoyuan Li ¹, Xu Liu ¹, Sixian Weng¹, Yan Yin ¹,
Qinchao Wu¹, Yijie Liu ¹, Zhipeng Hu¹, Hai Gao ¹, Ran Xiong¹, Zhuo Liang¹, Tao
Zhang ¹, Xin Quan,^{2*} Yunlong Wang ^{1*}

Lili Wang and Yanguang Li contributed equally as co-first authors for this article

* Yunlong Wang and Xin Quan contributed equally as co-corresponding authors

Affiliation

¹. Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

². Echocardiography Department, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Address for Correspondence

Yunlong Wang, E-mail: yunlong76818@126.com

Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, No. 2 Anzhen Rd, Chaoyang District, Beijing 100029, China.

Xin Quan, E-mail: xquan@hotmail.com

Echocardiography Department. State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81970272, No. 82300349).

Author Disclosures

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Acknowledgements

We thank all the investigators, staff, and participants of the CABANA study for their valuable contributions. This manuscript was prepared using CABANA Research Materials obtained from the NHLBI.

Table S1. Component of the Frailty index

Component	Cut-off	Score	CABANA_Missing_Count
Laboratory measures			
1	Creatinine, umol/L <40 or >150	1	98
Comorbidities			
2	Hypertension	1	1
3	Diabetes mellitus	1	2
4	Transient ischemic attack	1	1
5	Myocardial infarction	1	0
6	PCI or CABG	1	0
7	Heart valvular disease	1	1
8	Cardiomyopathy	1	3
9	Implanted device	1	1
10	Peripheral Thromboembolic events	1	1
11	Chronic lung disease	1	1
12	Renal disease (current or anticipated dialysis)	1	1
13	Thyroid disease	1	1
14	Cancer within the last 5 years	1	2
15	Hypercholesterolemia	1	2
16	Sleep apnea	1	1
17	Esophageal disease (i.e., reflux)	1	1
18	Atrial fibrillation	1	0
19	Smoking status	Never: 0 Former: 0.5 Current: 1	6
20	Alcohol	Never: 0 Former: 0.5 Current: 1	5
Other measures			
21	Overweight / Obesity	BMI $\geq$ 25 but <30 kg/m ² 0.5 BMI $\geq$ 30 kg/m ² 1	34
22	Underweight	BMI < 18.5 kg/m ² 1	34
23	SBP <90 or >140 mmHg	1	24
24	DBP >90 mmHg	1	28
25	Pulse pressure >55 mmHg	1	36
Quality of life measures			
26	Self-care	I have no problems with	33

		self-care 0 I have some problems washing or dressing myself 0.5 I am unable to wash or dress myself 1	
27	Mobility	I have no problems in walking about 0 I have some problems in walking about 0.5 I am confined to bed 1	33
28	Usual activities (e.g., work, study, housework, family, or leisure activities)	I have no problems with performing my usual activities 0 I have some problems with performing my usual activities 0.5 I am unable to perform my usual activities 1	33
29	Pain/discomfort	I have no pain or discomfort 0 I have moderate pain or discomfort 0.5 I have extreme pain or discomfort 1	33
30	Anxiety/depression	I am not anxious or depressed 0 I am moderately anxious or depressed 0.5 I am extremely anxious or depressed 1	33

Table S2. Baseline characteristics by frailty status and treatment subgroups (per-protocol)

	Frail				Non-frail				<i>P</i> 3
	Overall (N=1378)	Catheter ablation (N=664)	Drug therapy (N=714)	<i>P</i> 1	Overall (N=692)	Catheter ablation (N=319)	Drug therapy (N=373)	<i>P</i> 2	
Sex, N (%)				0.611				0.544	0.174
Female	498 (36.1)	245 (36.9)	253 (35.4)		272 (39.3)	121 (37.9)	151 (40.5)		
Male	880 (63.9)	419 (63.1)	461 (64.6)		420 (60.7)	198 (62.1)	222 (59.5)		
Age, N (%)				0.325				0.754	0.052
<65	490 (35.6)	226 (34.0)	264 (37.0)		231 (33.4)	106 (33.2)	125 (33.5)		
65–74	683 (49.6)	339 (51.1)	344 (48.2)		379 (54.8)	175 (54.9)	204 (54.7)		
≥75	205 (14.9)	99 (14.9)	106 (14.8)		82 (11.8)	38 (11.9)	44 (11.8)		
Race, N (%)				0.570				0.671	<0.001
Black	58 (4.2)	24 (3.6)	34 (4.8)		12 (1.7)	6 (1.9)	6 (1.6)		
Other	27 (2.0)	13 (2.0)	14 (2.0)		52 (7.5)	21 (6.6)	31 (8.3)		
White	1293 (93.8)	627 (94.4)	666 (93.3)		628 (90.8)	292 (91.5)	336 (90.1)		
BMI, kg/m²	32.1 (6.1)	31.9 (6.0)	32.3 (6.2)	0.194	28.5 (5.3)	28.4 (4.8)	28.7 (5.8)	0.472	<0.001
AF severity, N (%)				0.107				0.283	0.021
0	121 (8.8)	56 (8.5)	65 (9.1)		85 (12.3)	33 (10.4)	52 (14.0)		
1	198 (14.4)	79 (12.0)	119 (16.7)		117 (17.0)	64 (20.1)	53 (14.2)		
2	426 (31.0)	201 (30.4)	225 (31.6)		233 (33.8)	109 (34.3)	124 (33.3)		
3	525 (38.3)	272 (41.1)	253 (35.6)		222 (32.2)	95 (29.9)	127 (34.1)		
4	102 (7.4)	53 (8.0)	49 (6.9)		33 (4.8)	17 (5.3)	16 (4.3)		
NYHA class, N (%)				0.336				0.286	0.037

I	165 (11.9)	84 (12.6)	81 (11.3)		96 (13.9)	51 (16.0)	45 (12.1)		
II/III	515 (37.3)	238 (35.8)	277 (38.8)		216 (31.2)	99 (31.3)	117 (31.4)		
Medical history, N (%)									
Hypertension	1239 (89.9)	591 (89.0)	648 (90.8)	0.323	430 (62.1)	185 (58.0)	245 (65.7)	0.045	<0.001
Diabetes mellitus	461 (33.5)	219 (33.0)	242 (33.9)	0.763	58 (8.4)	23 (7.2)	35 (9.4)	0.373	<0.001
CVA	88 (6.4)	41 (6.2)	47 (6.6)	0.842	31 (4.5)	20 (6.3)	11 (2.9)	0.055	0.097
TIA	99 (7.2)	46 (6.9)	53 (7.4)	0.802	20 (2.9)	12 (3.8)	8 (2.1)	0.299	<0.001
History of HF	245 (17.8)	117 (17.6)	128 (17.9)	0.938	62 (9.0)	28 (8.8)	34 (9.1)	0.974	<0.001
Frail index	0.27 [0.23, 0.32]	0.27 [0.23, 0.32]	0.27 [0.24, 0.32]	0.021	0.17 [0.15, 0.20]	0.17 [0.15, 0.20]	0.17 [0.15, 0.18]	0.599	<0.001
CHA₂DS₂-VASc	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]	3.0 [2.0, 3.0]	0.882	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	0.089	<0.001
Type of AF				0.984				0.224	0.091
Long-standing persistent	139 (10.1)	66 (9.9)	73 (10.2)		60 (8.7)	34 (10.7)	26 (7.0)		
Persistent	573 (41.6)	277 (41.7)	296 (41.5)		322 (46.5)	144 (45.1)	178 (47.7)		
Paroxymal	666 (48.3)	321 (48.3)	345 (48.3)		310 (44.8)	141 (44.2)	169 (45.3)		
QoL measurement									
MAFSI Frequency	12.5 (6.4)	12.4 (6.2)	12.6 (6.5)	0.478	10.4 (5.8)	10.4 (5.8)	10.4 (5.7)	0.895	<0.001
MAFSI Severity	9.9 (5.1)	9.9 (5.1)	9.9 (5.2)	0.884	8.3 (4.7)	8.4 (4.7)	8.2 (4.7)	0.759	<0.001
EQ5D	67.7 (17.5)	68.4 (17.9)	67.1 (17.1)	0.168	73.4 (15.9)	72.9 (16.5)	73.9 (15.4)	0.384	<0.001

Data are presented as mean (standard derivation), median [interquartile range], or number (percentage)

P1 indicate differences between catheter ablation and drug therapy within patients with frailty.

P2 indicates differences between catheter ablation and drug therapy within patients with non-frailty.

P3 indicates differences between frail and non-frail groups.

Abbreviation: NYHA, New York Heart Association; CVA, cerebral vascular accident; TIA, transient ischemic attack; AF, atrial fibrillation; QoL, quality of life; BMI, body mass index. MAFSI, Mayo AF-Specific Symptom Inventory; EQ5D, Euro-QoL five dimensions questionnaire.

Table S3. Quality of Life Measures among frail patients according to treatment subgroups (intention-to-treat)

Follow-up Point	Drug Therapy			Catheter Ablation		
	Mean (SD)	Median [IQR]	No.	Mean (SD)	Median [IQR]	No.
MAFSI Frequency Score						
Baseline	12.65 (6.54)	12 [8,17]	696	12.39 (6.27)	12 [8,17]	654
3mo	9.91 (6.74)	9 [4,14]	586	7.64 (6.05)	7 [3,12]	580
12mo	8.88 (6.47)	8 [3,13]	535	6.8 (6.14)	5 [2,10]	532
24mo	8.63 (6.67)	8 [3,13]	458	6.5 (5.75)	5 [2,10]	489
36mo	8.39 (6.69)	7 [3,14]	351	6.86 (5.88)	6 [2,11]	373
48mo	7.78 (6.51)	7 [2,11]	261	7.09 (6.38)	6 [1,12]	281
60mo	7.81 (6.28)	6.5 [3,12]	182	6.6 (5.92)	6 [1,10]	187
MAFSI Severity Score						
Baseline	9.94 (5.17)	10 [6,14]	696	9.86 (5.03)	9 [6,13]	654
3mo	7.88 (5.44)	7 [3,12]	586	6.1 (4.89)	5 [2,9]	580
12mo	7.19 (5.24)	6 [3,11]	535	5.36 (4.9)	4 [1,8]	532
24mo	6.79 (5.26)	6 [2,10]	458	5.19 (4.6)	4 [2,8]	489
36mo	6.5 (5.24)	6 [2,10]	351	5.38 (4.65)	4 [2,8]	373
48mo	6.06 (5.07)	5 [2,9]	261	5.45 (4.81)	4 [1,8]	281
60mo	6.2 (4.98)	5 [2,9]	182	5.31 (4.91)	4 [1,7.25]	187

Abbreviation: MAFSI, Mayo AF-Specific Symptom Inventory; SD, standard deviation; IQR, interquartile range.

Table S4. Quality of Life Measures among patients with non-frail groups according to treatment subgroups (intention-to-treat)

Follow-up Point	Drug Therapy			Catheter Ablation		
	Mean (SD)	Median [IQR]	No.	Mean (SD)	Median [IQR]	No.
MAFSI Frequency Score						
Baseline	10.38 (5.71)	10 [6,14]	357	10.31 (5.77)	10 [6,14]	345
3mo	6.69 (5.41)	5 [2,10]	303	6.54 (5.55)	6 [2,10]	278
12mo	6.47 (5.54)	5 [2,10]	291	5.36 (5.53)	4 [1,8]	260
24mo	6.67 (5.83)	5 [2,10]	264	5.34 (5.43)	3 [1,9]	237
36mo	5.85 (5.55)	5 [1,9]	208	5.32 (5.53)	3 [1,8]	178
48mo	5.8 (5.36)	4 [1.25,9]	158	5.05 (5.09)	3 [1,7]	129
60mo	5.63 (5.91)	4 [1,8]	113	3.75 (4.49)	2 [0,5]	87
MAFSI Severity Score						
Baseline	8.24 (4.7)	8 [5,11]	357	8.29 (4.66)	8 [5,11]	345
3mo	5.58 (4.53)	5 [2,9]	303	5.38 (4.61)	5 [1,8]	278
12mo	5.49 (4.68)	4 [2,8]	291	4.46 (4.58)	3 [1,7]	260
24mo	5.38 (4.6)	4 [2,8]	264	4.37 (4.44)	3 [1,7]	237
36mo	4.84 (4.62)	4 [1,8]	208	4.42 (4.42)	3 [1,7.75]	178
48mo	4.68 (4.25)	4 [1,7]	158	4.23 (4.37)	3 [1,7]	129
60mo	4.64 (4.73)	3 [1,6]	113	3.28 (3.96)	2 [0,5]	87

Abbreviation: MAFSI, Mayo AF-Specific Symptom Inventory; SD, standard deviation; IQR, interquartile range.

Table S5. Quality of Life Measures among patients with frailty according to treatment subgroups (per-protocol)

Follow-up Point	Drug Therapy			Catheter Ablation		
	Mean (SD)	Median [IQR]	No.	Mean (SD)	Median [IQR]	No.
MAFSI Frequency Score						
Baseline	12.65 (6.54)	12 [8,17]	696	12.4 (6.24)	12 [8,17]	654
3mo	9.91 (6.74)	9 [4,14]	586	7.58 (6.02)	7 [3,11]	580
12mo	8.88 (6.47)	8 [3,13]	535	6.73 (6.16)	5 [2,10]	532
24mo	8.63 (6.67)	8 [3,13]	458	6.51 (5.69)	5 [2,10]	489
36mo	8.39 (6.69)	7 [3,14]	351	6.84 (5.81)	6 [2,11]	373
48mo	7.78 (6.51)	7 [2,11]	261	7.15 (6.4)	6 [1,12]	281
60mo	7.81 (6.28)	6.5 [3,12]	182	6.48 (5.74)	6 [1,10]	187
MAFSI Severity Score						
Baseline	9.94 (5.17)	10 [6,14]	696	9.9 (5.08)	9 [6,14]	654
3mo	7.88 (5.44)	7 [3,12]	586	6.09 (4.91)	5 [2,9]	580
12mo	7.19 (5.24)	6 [3,11]	535	5.3 (4.89)	4 [1,8]	532
24mo	6.79 (5.26)	6 [2,10]	458	5.18 (4.5)	4 [2,8]	489
36mo	6.5 (5.24)	6 [2,10]	351	5.38 (4.56)	5 [2,8]	373
48mo	6.06 (5.07)	5 [2,9]	261	5.49 (4.8)	5 [1,8]	281
60mo	6.2 (4.98)	5 [2,9]	182	5.24 (4.8)	4 [1,7]	187

Abbreviation: MAFSI, Mayo AF-Specific Symptom Inventory; SD, standard deviation; IQR, interquartile range.

Table S6. Quality of Life Measures among patients with non-frailty according to treatment subgroups (per-protocol)

Follow-up Point	Drug Therapy			Catheter Ablation		
	Mean (SD)	Median [IQR]	No.	Mean (SD)	Median [IQR]	No.
MAFSI Frequency Score						
Baseline	10.38 (5.71)	10 [6,14]	357	10.43 (5.82)	10 [6,14]	306
3mo	6.69 (5.41)	5 [2,10]	303	6.59 (5.58)	6 [2,10]	261
12mo	6.47 (5.54)	5 [2,10]	291	5.24 (5.46)	3 [1,8]	241
24mo	6.67 (5.83)	5 [2,10]	264	5.3 (5.39)	3 [1,9]	220
36mo	5.85 (5.55)	5 [1,9]	208	5.44 (5.59)	3 [1,8]	162
48mo	5.8 (5.36)	4 [1.25,9]	158	4.84 (4.99)	3 [1,7]	116
60mo	5.63 (5.91)	4 [1,8]	113	3.66 (4.41)	2 [0,5]	79
MAFSI Severity Score						
Baseline	8.24 (4.7)	8 [5,11]	357	8.35 (4.66)	8 [5,11]	306
3mo	5.58 (4.53)	5 [2,9]	303	5.48 (4.66)	5 [2,8]	261
12mo	5.49 (4.68)	4 [2,8]	291	4.43 (4.58)	3 [1,7]	241
24mo	5.38 (4.6)	4 [2,8]	264	4.41 (4.48)	3 [1,7]	220
36mo	4.84 (4.62)	4 [1,8]	208	4.51 (4.49)	3 [1,8]	162
48mo	4.68 (4.25)	4 [1,7]	158	4.09 (4.34)	2.5 [1,7]	116
60mo	4.64 (4.73)	3 [1,6]	113	3.22 (3.99)	2 [0,5]	79

Abbreviation: MAFSI, Mayo AF-Specific Symptom Inventory; SD, standard deviation; IQR, interquartile range.

Table S7. Effects of catheter ablation compared with drug therapy (per-protocol) on the primary endpoint, all-cause death, and HF hospitalization according to frailty status among patients with paroxysmal AF.

	HR (95% CI)	P value	P for interaction
Primary endpoint			
Overall	0.60(0.36-1.00)	0.052	0.651
Non-frail	0.79 (0.25-2.50)	0.689	
Frail	0.54 (0.30-0.95)	0.034	
All-cause death			
Overall	0.67 (0.36-1.23)	0.197	0.700
Non-frail	0.42 (0.08-2.19)	0.306	
Frail	0.62 (0.31-1.22)	0.165	
HF hospitalization			
Overall	0.66 (0.35-1.24)	0.197	0.647
Non-frail	0.45 (0.09-2.31)	0.337	
Frail	0.64 (0.32-1.30)	0.647	

Table S8. Effects of catheter ablation compared with drug therapy (per-protocol) on the primary endpoint, all-cause death, and HF hospitalization according to frailty status among patients with persistent AF.

	HR (95% CI)	P value	P for interaction
Primary endpoint			
Overall	0.79 (0.53-1.18)	0.244	0.946
Non-frail	0.76 (0.30-1.92)	0.558	
Frail	0.77 (0.50-1.20)	0.253	
All-cause death			
Overall	0.66 (0.41-1.08)	0.097	0.634
Non-frail	0.52 (0.17-1.56)	0.245	
Frail	0.68 (0.40-1.17)	0.167	
HF hospitalization			
Overall	1.37 (0.94-2.02)	0.104	0.525
Non-frail	0.99 (0.35-2.83)	0.987	
Frail	1.42 (0.94-2.14)	0.100	

Table S9. Effects of catheter ablation compared with drug therapy (intention-to-treat) on the primary endpoint, all-cause death, and HF hospitalization according to frailty status among patients with paroxysmal AF.

	HR (95% CI)	P value	P for interaction
Primary endpoint			
Overall	0.73 (0.46-1.14)	0.161	0.178
Non-frail	1.32 (0.46-3.76)	0.609	
Frail	0.59 (0.36-0.97)	0.037	
All-cause death			
Overall	0.80 (0.45-1.42)	0.444	0.474
Non-frail	0.43 (0.09-2.14)	0.302	
Frail	0.82 (0.44-1.53)	0.526	
HF hospitalization			
Overall	1.35 (0.83-2.19)	0.223	0.719
Non-frail	1.68 (0.38-7.53)	0.497	
Frail	1.23 (0.74-2.05)	0.425	

Table S10. Effects of catheter ablation compared with drug therapy (intention-to-treat) on the primary endpoint, all-cause death, and HF hospitalization according to frailty status among patients with persistent AF.

	HR (95% CI)	P value	P for interaction
Primary endpoint			
Overall	0.84 (0.56-1.27)	0.404	0.672
Non-frail	0.73 (0.26-2.00)	0.538	
Frail	0.85 (0.54-1.33)	0.475	
All-cause death			
Overall	0.80 (0.49-1.30)	0.371	0.993
Non-frail	0.76 (0.25-2.33)	0.631	
Frail	0.78 (0.46-1.34)	0.372	
HF hospitalization			
Overall	1.01 (0.67-1.51)	0.973	0.220
Non-frail	0.54 (0.19-1.56)	0.254	
Frail	1.11 (0.71-1.74)	0.635	

Table S11. Effects of catheter ablation compared with drug therapy (per-protocol) on the primary endpoint, all-cause death, and HF hospitalization according to frailty status among patients with persistent AF. (*Frail was defined as FI > 0.25, non-frail was defined as FI ≤ 0.25).

	HR (95% CI)	P value	P for interaction
Primary endpoint			0.948
Non-frail*	0.72 (0.43-1.20)	0.207	
Frail*	0.68 (0.45-1.01)	0.054	
All-cause death			0.656
Non-frail*	0.60 (0.31-1.13)	0.112	
Frail*	0.68 (0.42-1.10)	0.115	
HF hospitalization			0.261
Non-frail*	0.82 (0.43-1.56)	0.547	
Frail*	1.24 (0.85-1.82)	0.268	

Table S12. Effects of catheter ablation compared with drug therapy (intention-to-treat) on the primary endpoint, all-cause death, and HF hospitalization according to frailty status among patients with paroxysmal AF. (*Frail was defined as FI ≥ 0.25, non-frail was defined as FI < 0.25).

	HR (95% CI)	P value	P for interaction
Primary endpoint			0.544
Non-frail*	0.95 (0.59-1.53)	0.828	
Frail*	0.78 (0.54-1.13)	0.185	
All-cause death			0.806
Non-frail*	0.80 (0.44-1.45)	0.458	
Frail*	0.87 (0.56-1.35)	0.540	
HF hospitalization			0.184
Non-frail*	0.87 (0.49-1.54)	0.625	
Frail*	1.37 (0.96-1.95)	0.081	

Figure S1. Effects of catheter ablation compared with drug therapy (per-protocol) on the primary endpoint, all-cause death, and HF hospitalization according to frailty status

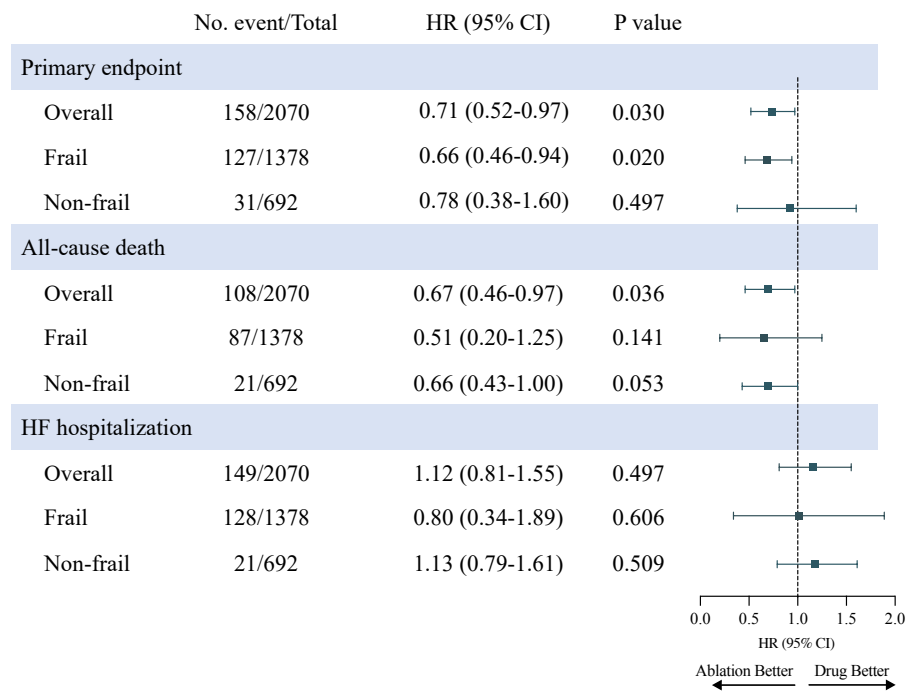


Figure S2. Kaplan–Meier Curves of the incidence of the primary endpoint comparison between catheter ablation and therapy (per-protocol) among all (A), frail (B) and non-frail patients (C)

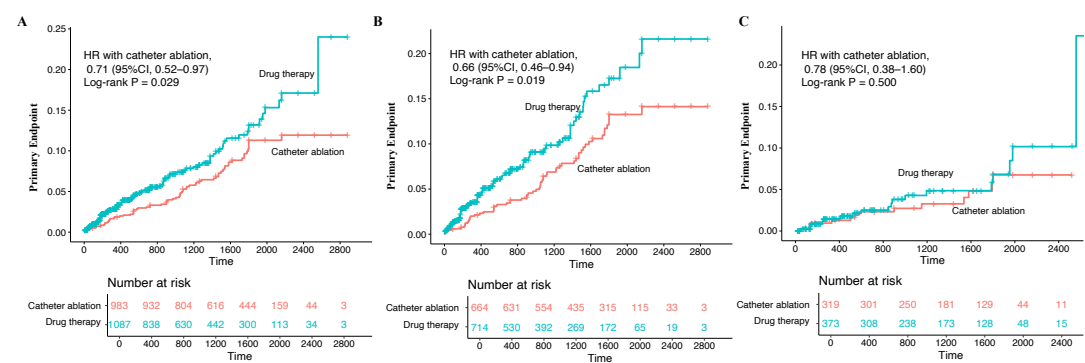


Figure S3. Effects of catheter ablation compared with drug therapy (per-protocol) on MAFSI Frequency score difference according to frailty status

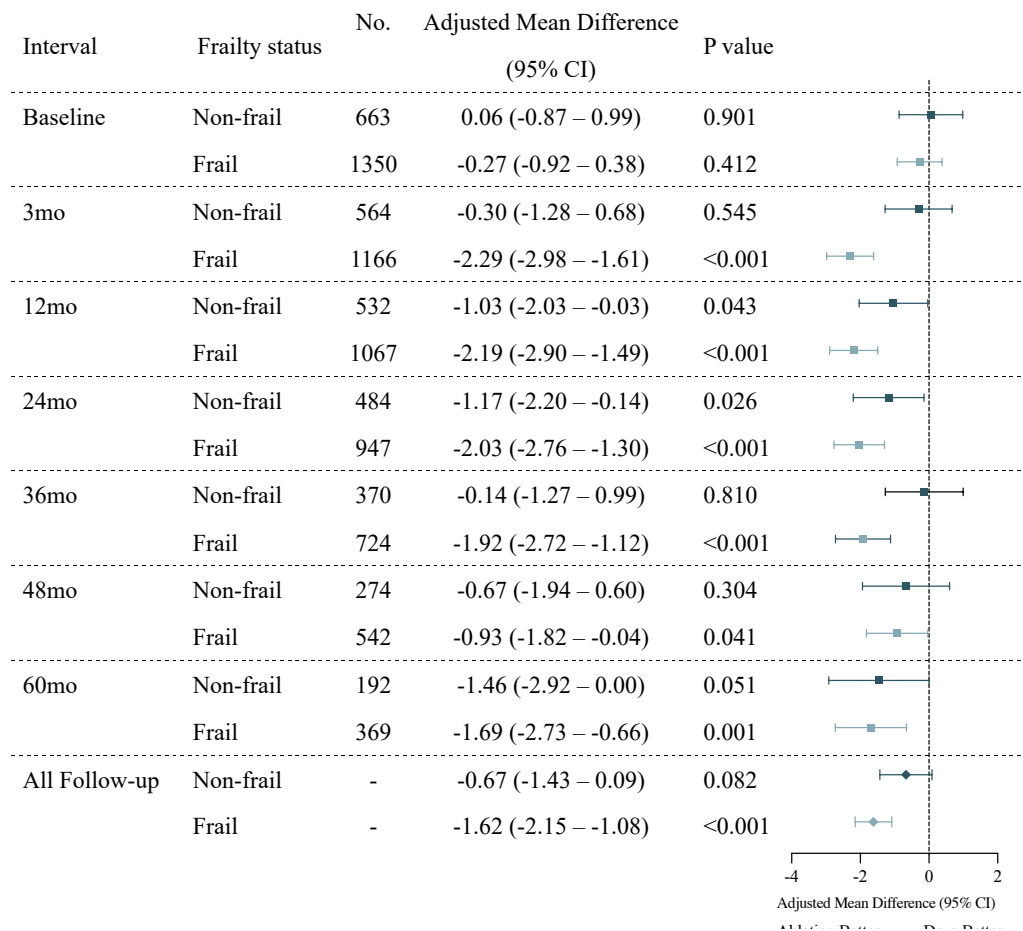


Figure S4. Effects of catheter ablation compared with drug therapy (per-protocol) on MAFSI Severity score difference according to frailty status

Abbreviation: CI, confidential interval.

