

## Early rhythm control in patients with atrial fibrillation and high comorbidity burden:

### Data Supplement

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**Supplementary Table 1** Demographic and clinical characteristics of the patients at baseline split by comorbidities into lower (CHA<sub>2</sub>DS<sub>2</sub>-VASc ≤4) and high (CHA<sub>2</sub>DS<sub>2</sub>-VASc >4) categories.

Characteristics	Overall, N = 2,789 <sup>1</sup>	Comorbidity burden (CHA <sub>2</sub> DS <sub>2</sub> -VASc score)		p-value <sup>2</sup>
		Low (<4) N = 1,696 <sup>1</sup>	High (≥4) N = 1,093 <sup>1</sup>	
Age	70 (8)	67 (8)	75 (7)	<0.001
Gender				<0.001
Female	1,293 / 2,789 (46%)	628 / 1,696 (37%)	665 / 1,093 (61%)	
Male	1,496 / 2,789 (54%)	1,068 / 1,696 (63%)	428 / 1,093 (39%)	
Body Mass Index (calculated) [kg/m <sup>2</sup> ]	29.3 (5.4)	29.3 (5.4)	29.1 (5.3)	0.31
AF type				0.96
First episode	1,048 / 2,785 (38%)	641 / 1,694 (38%)	407 / 1,091 (37%)	
Paroxysmal	994 / 2,785 (36%)	603 / 1,694 (36%)	391 / 1,091 (36%)	
Persistent or long-standing persistent	743 / 2,785 (27%)	450 / 1,694 (27%)	293 / 1,091 (27%)	
Sinus rhythm at baseline	1,505 / 2,782 (54%)	954 / 1,692 (56%)	551 / 1,090 (51%)	0.005
Median days since AF diagnosis (IQR)	36 (6, 112)	40 (7, 115)	28 (5, 110)	0.008
Absence of atrial fibrillation symptoms	801 / 2,633 (30%)	478 / 1,602 (30%)	323 / 1,031 (31%)	0.76
Previous pharmacological or electrical cardioversion	1,089 / 2,753 (40%)	685 / 1,675 (41%)	404 / 1,078 (37%)	0.055
<b>Concomitant cardiovascular conditions</b>				
Prior AF ablation	3 / 2,789 (0.1%)	0 / 1,696 (0%)	3 / 1,093 (0.3%)	0.93
Previous stroke or transient ischemic attack	328 / 2,789 (12%)	45 / 1,696 (2.7%)	283 / 1,093 (26%)	<0.001
At least mild cognitive impairment	1,166 / 2,667 (44%)	624 / 1,616 (39%)	542 / 1,051 (52%)	<0.001
Arterial hypertension	2,447 / 2,784 (88%)	1,412 / 1,693 (83%)	1,035 / 1,091 (95%)	<0.001
Systolic blood pressure [mmHg]	137 (19)	137 (19)	138 (20)	0.046
Diastolic blood pressure [mmHg]	81 (12)	82 (12)	80 (12)	<0.001
Stable heart failure	798 / 2,789 (29%)	322 / 1,696 (19%)	476 / 1,093 (44%)	<0.001
Chronic kidney disease of MDRF stage 3 or 4	351 / 2,789 (13%)	130 / 1,696 (7.7%)	221 / 1,093 (20%)	<0.001

Diabetes mellitus	694 / 2,784 (25%)	259 / 1,693 (15%)	435 / 1,091 (40%)	<0.001
Severe coronary artery diseases (prev. MI, CABG or PCI)	479 / 2,789 (17%)	145 / 1,696 (8.5%)	334 / 1,093 (31%)	<0.001
LVEF	59 (10)	60 (9)	58 (11)	<0.001
Diastolic LA diameter (maximal diameter) [mm]	44 (8)	44 (9)	44 (8)	0.14
<b>Medication at discharge</b>				
Oral anticoagulation with NOAC or VKA	2,517 / 2,782 (90%)	1,510 / 1,691 (89%)	1,007 / 1,091 (92%)	0.005
Digoxin or digitoxin	131 / 2,782 (4.7%)	71 / 1,691 (4.2%)	60 / 1,091 (5.5%)	0.056
Beta blockers	2,249 / 2,782 (81%)	1,353 / 1,691 (80%)	896 / 1,091 (82%)	0.60
ACE inhibitors or angiotensin II receptor blocker	1,932 / 2,782 (69%)	1,077 / 1,691 (64%)	855 / 1,091 (78%)	<0.001
Mineralocorticoid receptor antagonist	182 / 2,782 (6.5%)	60 / 1,691 (3.5%)	122 / 1,091 (11%)	<0.001
Diuretic	1,120 / 2,782 (40%)	543 / 1,691 (32%)	577 / 1,091 (53%)	<0.001
Statin	1,196 / 2,782 (43%)	574 / 1,691 (34%)	622 / 1,091 (57%)	<0.001
Platelet inhibitor	455 / 2,782 (16%)	214 / 1,691 (13%)	241 / 1,091 (22%)	<0.001
Oral antidiabetics	459 / 2,782 (16%)	177 / 1,691 (10%)	282 / 1,091 (26%)	<0.001
<b>Planned therapy for rhythm control at baseline</b>				
				0.86
AAD	1,268 / 2,789 (45%)	768 / 1,696 (45%)	500 / 1,093 (46%)	
Ablation	114 / 2,789 (4.1%)	72 / 1,696 (4.2%)	42 / 1,093 (3.8%)	
None	1,407 / 2,789 (50%)	856 / 1,696 (50%)	551 / 1,093 (50%)	
<sup>1</sup> Mean (SD) or Frequency with no./total no. (%)				
<sup>2</sup> p-values resulting from mixed linear regression models for metric variables and mixed (multinomial or ordinal) logistic regression models for categorical variables. For categorical variables with more than two categories (not ordinal) random effect is not included.				

AAD= Antiarrhythmic drug; ACE=Angiotensin converting enzyme; AF=Atrial fibrillation; CABG= Coronary artery bypass graft; IQR= Interquartile range; LA=Left atrium; LVEF= Left ventricular ejection fraction; MDRD= Modification of Diet in Renal Disease; MI=Myocardial infarction; NOAC= Novel oral anticoagulants; PCI= Percutaneous coronary intervention; SD= Standard deviation; VAK= Vitamin K antagonists.

**Supplementary Table 2**Number of nights spent in hospital according to CHA<sub>2</sub>DS<sub>2</sub>-VAsC score

Characteristics	CHA <sub>2</sub> DS <sub>2</sub> -VAsC score		p-value <sup>1</sup>
	Low, N = 1,696	High, N = 1,093	
Nights spent in hospital			<0.001
Median (IQR)	5 (0, 15)	8 (1, 26)	
Mean (SD)	14 (25)	21 (32)	
Nights spent in hospital per year			0.001
Median (IQR)	1.0 (0.0, 3.1)	2.0 (0.4, 6.0)	
Mean (SD)	4.3 (17.0)	7.2 (21.7)	
<sup>1</sup> p-values resulting from mixed linear regression models.			

SD = Standard deviation, IQR = Interquartile range

**Supplementary Table 3** Reduced list of events with deaths and life-threatening serious adverse events, including events that were judged to be potentially life-threatening by the authors. This excludes nonmajor bleedings, hospitalizations for atrial fibrillation, and drug-induced atrio-ventricular block and bradycardia. The table also excludes stroke as this was also a component of the primary efficacy outcome.

Outcome	Lower comorbidity burden (CHA <sub>2</sub> DS <sub>2</sub> -VASc Score <4)				High comorbidity burden (CHA <sub>2</sub> DS <sub>2</sub> -VASc Score ≥4)				p-value interaction
	ERC	UC	HR (95CI)	p-value	ERC	UC	HR (95CI)	p-value	
Death	66 (7.8)	70 (8.2)	0.97 (0.69, 1.36)	0.860	72 (13.1)	94 (17.3)	0.74 (0.54, 1.01)	0.0563	0.255
<i>Torsades de pointes</i>	0 (0)	0 (0)	<i>na</i>	<i>na</i>	1 (0.2)	0 (0)	Na (0, Inf)	0.9997	0.998
<i>Non-fatal cardiac arrest</i>	0 (0)	0 (0)	<i>na</i>	<i>na</i>	1(0.2)	1 (0.2)	1.03 (0.06, 16.4)	0.9856	>0.99
<i>Drug toxicity related to atrial fibrillation treatment</i>	7 (0.8)	2 (0.2)	3.57 (0.74, 17.19)	0.112	3 (0.5)	1 (0.2)	2.97 (0.31, 28.6)	0.3451	0.3451
Pericardial tamponade	1 (0.1)	0 (0)	<i>na</i> (0, Inf)	>0.99	2 (0.4)	0 (0)	<i>na</i> (0, Inf)	0.9996	>0.99
Major bleeding due to AF ablation	1 (0.1)	0 (0)	<i>na</i> (0, Inf)	>0.99	5 (0.9)	0 (0)	<i>na</i> (0, Inf)	0.9993	>0.99
<b>Occurrence of death or potentially life-threatening events</b>	<b>72 (8.5)</b>	<b>72 (8.5)</b>	<b>1.04 (0.75, 1.44)</b>	<b>0.833</b>	<b>82 (15)</b>	<b>96 (18)</b>	<b>0.84 (0.62, 1.13)</b>	<b>0.242</b>	<b>0.348</b>

AF= Atrial fibrillation; ERC= Early rhythm control, UC= Usual care

**Supplementary Table 4**Rhythm control chosen by treatment group and CHA<sub>2</sub>DS<sub>2</sub>-VASc score strata

	Lower comorbidity burden (CHA <sub>2</sub> DS <sub>2</sub> -VASc Score <4)		High comorbidity burden (CHA <sub>2</sub> DS <sub>2</sub> -VASc Score ≥4)	
	ERC	UC	ERC	UC
n	846	850	549	544
<b>Rhythm Control at BL</b>				
AF ablation	70 (8.3)	2 (0.2)	42 (7.7)	0 (0.0)
Dronedarone	132 (15.6)	0 (0.0)	101 (18.4)	1 (0.2)
Amiodarone	130 (15.4)	19 (2.2)	144 (26.2)	9 (1.7)
Flecainide	336 (39.7)	15 (1.8)	165 (30.1)	9 (1.7)
Propafenone	59 (7.0)	2 (0.2)	38 (6.9)	0 (0.0)
Other antiarrhythmic drug	74 (8.7)	1 (0.1)	32 (5.8)	1 (0.2)
None	45 (5.3)	811 (95.4)	27 (4.9)	524 (96.3)
<b>Rhythm Control at FU24</b>				
AF ablation	185 (21.9)	68 (8.0)	85 (15.5)	29 (5.3)
Dronedarone	50 (5.9)	4 (0.5)	33 (6.0)	1 (0.2)
Amiodarone	89 (10.5)	26 (3.1)	75 (13.7)	13 (2.4)
Flecainide	203 (24.0)	32 (3.8)	90 (16.4)	8 (1.5)
Propafenone	37 (4.4)	13 (1.5)	16 (2.9)	3 (0.6)
Other antiarrhythmic drug	27 (3.2)	2 (0.2)	18 (3.3)	4 (0.7)
None	255 (30.1)	705 (82.9)	232 (42.3)	486 (89.3)

BL = Baseline, FU= follow-up, AF= atrial fibrillation, ERC= Early rhythm control, UC= Usual care

**Supplementary Table 5** Key secondary outcomes compared between early rhythm control and usual care split into patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥4 and patients with a lower CHA<sub>2</sub>DS<sub>2</sub>-VASc score <4, Model-based differences for metric outcomes and odds ratios for dichotomous outcomes, and respective p-values were adjusted for baseline measurement and center as random effect and were estimated. The full analysis set without imputations was used as database.

Characteristic	CHA <sub>2</sub> DS <sub>2</sub> -VASc Score <4				CHA <sub>2</sub> DS <sub>2</sub> -VASc Score ≥4				Inter-action p-value
	Early rhythm control, N = 846	Usual care, N = 850	Adj Diff/OR [95% CI]	p-value	Early rhythm control, N = 549	Usual care, N = 544	Adj Diff/OR [95% CI]	p-value	
Change in LVEF	1.36 ± 9.51	0.612 ± 9.27	0.30 [-0.52, 1.12]	0.467	1.71 ± 10.1	1.01 ± 10.7	0.52 [-0.54, 1.59]	0.334	0.749
Change in EQ5D score	0.528 ± 17.4	0.474 ± 16.4	-0.22 [-1.96, 1.53]	0.806	2.85 ± 17.6	1.21 ± 17.4	1.97 [-0.33, 4.27]	0.093	0.137
Change in SF-12 Mental Score	0.667 ± 10.6	1.33 ± 9.75	-1.03 [-2.04, -0.02]	0.045	0.781 ± 10.8	2.02 ± 10.8	-0.68 [-2.03, 0.67]	0.323	0.680
Change in SF-12 Physical Score	0.456 ± 8.51	0.278 ± 7.83	0.25 [-0.62, 1.11]	0.575	-0.004 ± 8.48	-0.345 ± 8.75	0.46 [-0.69, 1.61]	0.432	0.770
Change in MoCA	0.231 ± 3.22	-0.003 ± 3.08	0.06 [-0.25, 0.37]	0.706	-0.099 ± 3.39	0.297 ± 3.35	-0.34 [-0.75, 0.07]	0.105	0.130
Sinus rhythm + Pacing	587 / 696 (84.3%)	458 / 719 (63.7%)	3.57 [2.71, 4.69]	<0.001	334 / 426 (78.4%)	229 / 416 (55.0%)	3.48 [2.51, 4.82]	<0.001	0.903
Asymptomatic	549 / 721 (76.1%)	557 / 737 (75.6%)	0.99 [0.76, 1.29]	0.958	312 / 438 (71.2%)	293 / 434 (67.5%)	1.26 [0.92, 1.74]	0.155	0.262

LVEF= Left ventricular ejection fraction; EQ-5D score European Quality of Life 5 Dimensions score; SF-12 Short Form Health survey 12-items; MoCA score Montreal Cognitive Assessment Score.

**Supplementary Table 6** Demographic and clinical characteristics of the patients at baseline split by comorbidities excluding sex into low (CHA<sub>2</sub>DS<sub>2</sub>-VA ≤4) and high (CHA<sub>2</sub>DS<sub>2</sub>-VA >4) categories.

Characteristics	Low CHA <sub>2</sub> DS <sub>2</sub> -VA Score		High CHA <sub>2</sub> DS <sub>2</sub> -VA Score	
	ERC, N = 1,008 <sup>1</sup>	UC, N = 1,018 <sup>1</sup>	ERC, N = 387 <sup>1</sup>	UC, N = 376 <sup>1</sup>
Age	68 (8.4)	69 (8.0)	75 (6.7)	75 (6.8)
Gender				
Female	470/1,008 (47%)	488/1,018 (48%)	175/387 (45%)	160/376 (43%)
Male	538/1,008 (53%)	530/1,018 (52%)	212/387 (55%)	216/376 (57%)
Body Mass Index (calculated) [kg/m <sup>2</sup> ]	29.2 (5.4)	29.2 (5.4)	29.2 (5.3)	29.5 (5.3)
AF type				
First episode	386/1,006 (38%)	385/1,018 (38%)	142/385 (37%)	135/376 (36%)
Paroxysmal	360/1,006 (36%)	364/1,018 (36%)	141/385 (37%)	129/376 (34%)
Persistent or long-standing persistent	260/1,006 (26%)	269/1,018 (26%)	102/385 (26%)	112/376 (30%)
Sinus rhythm at baseline	559/1,004 (56%)	564/1,018 (55%)	203/385 (53%)	179/375 (48%)
Median days since AF diagnosis (IQR)	36.0 (6.0, 115.0)	40.0 (6.0, 108.0)	34.5 (6.0, 107.0)	26.5 (4.8, 113.2)
Absence of AF symptoms	277/945 (29%)	288/974 (30%)	118/360 (33%)	118/354 (33%)
Previous pharmacological or electrical cardioversion	404/988 (41%)	399/1,015 (39%)	142/376 (38%)	144/374 (39%)
Concomitant cardiovascular conditions				
Prior AF ablation	0/1,008 (0%)	0/1,018 (0%)	0/387 (0%)	3/376 (0.8%)
Previous stroke or transient ischemic attack	31/1,008 (3.1%)	27/1,018 (2.7%)	144/387 (37%)	126/376 (34%)
At least mild cognitive impairment	398/953 (42%)	391/979 (40%)	184/373 (49%)	193/362 (53%)
Arterial hypertension	862/1,005 (86%)	859/1,018 (84%)	365/385 (95%)	361/376 (96%)
Systolic blood pressure [mmHg]	137 (19.2)	137 (19.1)	135 (19.9)	139 (19.7)
Diastolic blood pressure [mmHg]	82 (12.0)	82 (12.0)	79 (12.0)	80 (12.0)
Stable heart failure	196/1,008 (19%)	201/1,018 (20%)	200/387 (52%)	201/376 (53%)
Chronic kidney disease of MDRF stage 3 or 4	92/1,008 (9.1%)	95/1,018 (9.3%)	80/387 (21%)	84/376 (22%)
Diabetes mellitus	177/1,005 (18%)	166/1,018 (16%)	174/385 (45%)	177/376 (47%)
Severe coronary artery diseases (prev. MI, CABG or PCI)	88/1,008 (8.7%)	80/1,018 (7.9%)	155/387 (40%)	156/376 (41%)
LVEF	59.4 (9.0)	59.7 (9.5)	57.2 (11.4)	56.1 (11.7)



Diastolic LA diameter (maximal diameter) [mm]	43.6 (8.5)	43.7 (8.6)	44.4 (8.2)	44.8 (8.4)
Cognitive function (MoCA) at baseline	25.7 (3.6)	25.8 (3.6)	24.8 (3.9)	24.5 (4.1)
EQ5D Visual Analogue Scale at baseline	73.5 (16.3)	73.1 (16.4)	66.9 (16.6)	67.5 (17.1)
SF12 Mental Component Baseline	50.3 (9.9)	50.4 (9.8)	50.5 (9.7)	49.3 (9.9)
SF12 Physical Component Baseline	45.8 (8.5)	45.4 (8.6)	41.7 (8.6)	42.2 (8.3)
Medication at discharge				
Oral anticoagulation with NOAC or VKA	909/1,004 (91%)	912/1,017 (90%)	358/385 (93%)	338/376 (90%)
Digoxin or digitoxin	33/1,004 (3.3%)	60/1,017 (5.9%)	13/385 (3.4%)	25/376 (6.6%)
Beta blockers	760/1,004 (76%)	858/1,017 (84%)	298/385 (77%)	333/376 (89%)
ACE inhibitors or angiotensin II receptor blocker	647/1,004 (64%)	672/1,017 (66%)	306/385 (79%)	307/376 (82%)
Mineralocorticoid receptor antagonist	43/1,004 (4.3%)	51/1,017 (5.0%)	47/385 (12%)	41/376 (11%)
Diuretic	350/1,004 (35%)	349/1,017 (34%)	209/385 (54%)	212/376 (56%)
Statin	361/1,004 (36%)	329/1,017 (32%)	267/385 (69%)	239/376 (64%)
Platelet inhibitor	124/1,004 (12%)	127/1,017 (12%)	105/385 (27%)	99/376 (26%)
Oral antidiabetics	119/1,004 (12%)	118/1,017 (12%)	109/385 (28%)	113/376 (30%)
Planned therapy for rhythm control at baseline				
AAD	877/1,008 (87%)	45/1,018 (4.4%)	334/387 (86%)	12/376 (3.2%)
Ablation	80/1,008 (7.9%)	2/1,018 (0.2%)	32/387 (8.3%)	0/376 (0%)
None	51/1,008 (5.1%)	971/1,018 (95%)	21/387 (5.4%)	364/376 (97%)
<sup>1</sup> Mean (SD) or Frequency with no./total no. (%)				

AAD= Antiarrhythmic drug; AF= atrial fibrillation, ACE= Angiotensin Converting Enzyme; CABG= Coronary artery bypass graft; EHRA score= European Heart Rhythm Association score for assessment of atrial fibrillation symptoms score; EQ-5D score= European Quality of Life 5 Dimensions score; ERC= Early rhythm control; IQR= Interquartile range; LVEF= Left ventricular ejection fraction; LA= left atrium; MI= Myocardial infarction; MoCA score= Montreal Cognitive Assessment Score. MDRD= Modification of Diet in Renal Disease; NOAC= Novel oral anticoagulants; PCI= Percutaneous coronary intervention; SD= standard deviation; SF-12= Short Form Health survey 12-items; UC= Usual care; VKA= Vitamin K antagonists.

**Supplementary Table 7** Efficacy of early rhythm control and usual care by randomized group and by CHA<sub>2</sub>DS<sub>2</sub>-VA score, split into patients with CHA<sub>2</sub>DS<sub>2</sub>-VA score ≥4 and patients with a lower CHA<sub>2</sub>DS<sub>2</sub>-VA score <4

	CHA <sub>2</sub> DS <sub>2</sub> -VA group	Early rhythm control	Usual care	interaction p-value	HR (95% CI)	p-value
<b>Primary outcome (First occurrence of composite)</b>	<4	143/1008 (14.2%)	175/1018 (17.2%)	0.250	0.83 (0.66, 1.04)	0.098
	≥4	106/387 (27.4%)	141/376 (37.5%)		0.68 (0.53, 0.88)	0.003
<b>Death from cardiovascular causes</b>	<4	35/1008 (3.5%)	46/1018 (4.5%)	0.329	0.79 (0.51, 1.22)	0.287
	≥4	32/387 (8.3%)	48/376 (12.8%)		0.60 (0.38, 0.95)	0.029
<b>Stroke</b>	<4	25/1008 (2.5%)	33/1018 (3.2%)	0.273	0.78 (0.46, 1.31)	0.352
	≥4	15/387 (3.9%)	29/376 (7.7%)		0.50 (0.27, 0.94)	0.031
<b>Hospitalization with worsening of HF</b>	<4	75/1008 (7.4%)	92/1018 (9.0%)	0.552	0.82 (0.60, 1.12)	0.208
	≥4	64/387 (16.5%)	77/376 (20.5%)		0.75 (0.54, 1.05)	0.096
<b>Hospitalization with ACS</b>	<4	31/1008 (3.1%)	41/1018 (4.0%)	0.691	0.78 (0.49, 1.25)	0.303
	≥4	22/387 (5.7%)	24/376 (6.4%)		0.87 (0.48, 1.55)	0.626
<b>EAST Primary safety endpoint</b>	<4	139/1008 (13.8%)	120/1018 (11.8%)	0.044	1.23 (0.97, 1.58)	0.092
	≥4	92/387 (23.8%)	103/376 (27.4%)		0.87 (0.66, 1.16)	0.337
<b>CABANA-like endpoint</b>	<4	90/1008 (8.9%)	100/1018 (9.8%)	0.221	0.93 (0.70, 1.24)	0.630
	≥4	72/387 (18.6%)	91/376 (24.2%)		0.75 (0.55, 1.03)	0.073

HF= Heart failure; ACS= Acute coronary syndrome; EAST indicates Early Treatment for Atrial Fibrillation for Stroke Prevention. CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation.