Clinical characteristics of heart failure patients undergoing atrial fibrillation ablation today in Europe. Data from the atrial fibrillation registries of the European Society of Cardiology and the European Heart Rhythm Association

Temporelli, Pier Luigi; Tilz, Roland R; Arbelo, Elena; Dagres, Nikolaos; Laroche, Cécile; Crijns, Harry J; Blomstrom-Lundqvist, Carina; Kirchhof, Paulus; Lip, Gregory Y H; Boriani, Giuseppe; Pokushalov, Evengy; Nakou, Eleni; Brugada, Josep; Tavazzi, Luigi

DOI:
10.1002/ejhf.1458

doi:10.1002/ejhf.1458

Clinical characteristics of heart failure patients undergoing atrial fibrillation ablation today in Europe. Data from the atrial fibrillation registries of the European Society of Cardiology and the European Heart Rhythm Association

Over the past three decades, catheter ablation of atrial fibrillation (AF) has evolved from an investigational procedure to its current role as a standard treatment option. Current guidelines recommend catheter ablation for symptomatic AF patients, preferring non-pharmacological therapy or resistant to antiarrhythmic drugs.[1] However, which patients with AF and heart failure (HF) are actually referred for AF ablation in clinical practice today is still unclear, and the indication criteria are likely to be reconsidered by cardiologists in the light of the recent published literature.

A recent non individual-based meta-analysis of six small randomized controlled trials (RCTs) including 775 HF patients, most with persistent AF, mean age 55–64 years, reduced left ventricular ejection fraction (EF) (mean 28.3%), and a mean follow-up longer than 12 months, showed an improvement of both EF and patient functional capacity associated with a significant reduction of both readmission and death rates.[2] Since then, results of two larger RCTs have been reported. The CASTLE-AF trial, including 339 HF patients (EF $\leq$35%) out of 3013 patients assessed for enrolment over a period of 8 years, showed a lower rate of the combined endpoint of death and hospitalization for HF with AF ablation than medical therapy (hazard ratio 0.62, 95% confidence interval 0.43–0.87).[3] The CABANA trial comparing AF ablation vs. antiarrhythmic pharmacological therapy included 2204 AF patients, with only 15% having a history of congestive HF (the results have been reported but are yet unpublished).[4] Based on the original intention-to-treat trial design, the results were neutral, however, in the on-treatment analysis, due to an (expected) shift of approximately one third of patients randomized to drug treatment to the ablation arm, with a significant benefit on the primary endpoint in the ablation group (7% vs. 10.9%; hazard ratio 0.67, 95% confidence interval 0.50–0.89).

An attempt to understand which HF patients cardiologists actually do select as candidates for AF ablation is therefore worthwhile, and prospective registries on AF recently conducted by the European Society of Cardiology (ESC) and the European Heart Rhythm Association may offer such an opportunity. This applies in particular to two published registries, the Atrial Fibrillation Ablation (AFA) Registry aimed at providing an observational picture of contemporary real-world AF ablation strategy and its outcome[5] and the Atrial Fibrillation General Pilot (AFG) Registry[6] collected in Europe within approximately the same time frame, by partly overlapping centre networks, and conducted by the same ESC management team. In the AFA registry, most patients underwent a first ablation procedure, while 19% had a redo procedure. In the AFG registry, 7.6% of patients had undergone an AF ablation procedure before enrolment in the registry, while ablation was performed or planned at admission in 6.8% of patients. We specifically focused on the HF patients enrolled in both studies: 537 (14.9%) in AFA and 1382 (46.5%) in AFG, respectively.

The clinical characteristics of these HF cohorts are summarized in *Table 1*. AFA patients were a decade younger, had less prevalent cardiovascular risk factors (e.g. diabetes, hypercholesterolaemia, smoking habit) than AFG patients, and a lower risk of both stroke (CHA_2DS_2-VASc) and bleeding (HAS-BLED). While there were no differences in baseline blood pressure and gender ratio between the two cohorts, mean heart rate was faster in the general AF cohort than in ablated patients. Underlying or concomitant clinical disorders such as coronary and peripheral artery disease, valvular heart disease, previous transient ischaemic attack, chronic kidney and liver disease, and chronic obstructive pulmonary disease were less common in ablated patients than in the general AF population. As expected, the rate of paroxysmal AF was two-fold higher in the AFA HF patients, which were more symptomatic than the AFG HF patients.

AFA patients had smaller left atrial size and higher EF at echocardiographic imaging. Most AFA patients (77%) had a preserved EF ($\geq$ 50%, HFpEF), while those with mid-range EF (40–49%, HFmrEF) or reduced EF ($<$ 40%, HFrEF) were a relatively small minority (15% and 8%, respectively). The relative proportion of the EF phenotypes among AFG patients was more balanced (HFpEF 46%, HFmrEF 21%, HFrEF 33%). The clinical profile of each EF subtype of ablated patients was more favourable than that of the corresponding HF patients in the AFG registry (data not reported).

The few data reported above are descriptive, and the analysis only underscores a few major differences between the two AF cohorts. In fact, they are different by definition. In both groups, the setting is the same – the cardiology department – but the AFA patients were selected for an atrial ablation, whereas the AFG patients were seeking for clinical care. The differences between them outline the interventional niche reserved to co-morbid HF-AF patients in Europe today, which probably reflects a certain clinical cautiousness. The choice for intervention appears more focused on relieving AF-related symptoms than on an attempt to influence the clinical course of HF. Whether or not the most recent randomized trials[3,4] may prompt a more extensive use of AF ablation in HF patients is open to debate.[7,8] Besides other considerations, a potential limitation of the RCTs conducted so far is the uncertain representativeness of the patients enrolled. Organizational and methodological difficulties encountered in enrolling randomized patients and the consequent methodological adjustments inevitably impact on the representativeness of the study population. For instance, in our open AFA cohort, only 42 patients with EF $\leq$35% were included, and only nine of these had a cardioverter-defibrillator implanted (both entry criteria in the CASTLE-AF trial).

Conflict of interest: none declared.

Table 1 Clinical characteristics of heart failure patients in the Atrial Fibrillation Ablation Long-Term (AFA) Registry vs Atrial Fibrillation General Pilot Registry

	HF AFA ($n = 537$)	HF AFG ($n = 1382$)	*P*-value
Demographics			
Age, years [mean (SD)]	59.9 (8.9)	70.7 (10.8)	<0.001
Men, *n* (%)	339/537 (63.1)	816/1382 (59.0)	0.101
Body mass index > 30 kg/m^2, *n* (%)	215/515 (41.7)	422/1350 (31.3)	<0.001
Systolic blood pressure, mmHg [mean (SD)]/*n*	131.0 (17.3)/529	133.1 (23.4)/1382	0.203
Diastolic blood pressure, mmHg [mean (SD)]/*n*	81.1 (10.3)/529	79.3 (14.2)/1382	<0.001
Heart rate, b.p.m. [mean (SD)]/*n*	79.3 (24.7)/496	91.3 (28.8)/1375	<0.001
Cardiovascular risk factors, *n* (%)			
Diabetes mellitus	78/536 (14.6)	374/1373 (27.2)	<0.001
Hypertension	393/536 (73.3)	1034/1375 (75.2)	0.396
Smoking (present or former)	129/518 (24.9)	557/1337 (41.7)	<0.001
Hypercholesterolaemia	231/525 (44.0)	754/1352 (55.8)	<0.001
Ischaemic thromboembolic events	44/534 (8.2)	220/1362 (16.2)	<0.001
CHA_2DS_2-VASc score, *n* (%)			<0.001
1	67/532 (12.6)	54/1382 (3.9)	
2	176/532 (33.1)	168/1382 (12.2)	
3	159/532 (29.9)	250/1382 (18.1)	
4	75/532 (14.1)	339/1382 (24.5)	
≥ 5	54/532 (10.2)	571/1382 (41.3)	
HAS-BLED score, *n* (%)			
0	321/523 (61.4)	187/1382 (13.5)	<0.001
1	162/523 (31.0)	470/1382 (34.0)	
≥ 2	40/523 (7.6)	725/1382 (52.5)	<0.001
Type of AF			<0.001
Paroxysmal	302/537 (56.2)	319/1379 (23.1)	
Persistent	172/537 (32.0)	467/1379 (33.9)	
Long-standing persistent	63/537 (11.7)	120/1379 (8.7)	
Permanent	–	473/1379 (34.3)	
AF underlying disorder, *n* (%)			
Coronary artery disease	190/520 (36.5)	597/1200 (49.8)	<0.001
Dilated cardiomyopathy	47/536 (8.8)	305/1359 (22.4)	<0.001
Hypertensive cardiomyopathy	166 534 (31.1)	340/1365 (24.9)	0.006
Hypertrophic cardiomyopathy	13/537 (2.4)	80/1364 (5.9)	0.002
Valvular heart disease	104/534 (19.5)	1024/1350 (75.9)	<0.001
Hyperthyroidism	25/530 (4.7)	45/1303 (3.5)	0.201
Other cardiac disease	48/535 (9.0)	121/1295 (9.3)	0.803
Concomitant clinical conditions, *n* (%)			
Previous TIA	9/535 (1.7)	54/1354 (4.0)	0.012
Previous stroke	33/535 (6.2)	113/1364 (8.3)	0.119
Peripheral vascular disease	28/527 (5.3)	225/1347 (16.7)	<0.001
Chronic kidney disease	16/527 (3.0)	299/1373 (21.8)	<0.001
Liver disease	11/528 (2.1)	106/1375 (7.7)	<0.001
COPD	18/527 (3.4)	211/1364 (15.5)	<0.001
Haemorrhagic events	5/530 (0.9)	93/1361 (6.8)	<0.001
Malignancy	13/532 (2.4)	72/1324 (5.4)	0.005
EHRA score, *n* (%)			
1	3/536 (0.6)	514/1382 (37.2)	<0.001
2	229/536 (42.7)	339/1382 (24.5)	
3	257/536 (47.9)	425/1382 (30.8)	
4	47/536 (8.8)	104/1382 (7.5)	

Table 1 Continued

	HF AFA($n = 537$)	HF AFG($n = 1382$)	*P*-value
Associated symptoms, *n* (%)			
Palpitations	425/536 (79.3)	636/1382 (46.0)	<0.001
Fatigue	311/536 (58.0)	491/1382 (35.5)	<0.001
Dyspnoea	339/536 (63.2)	945/1382 (68.4)	0.082
Weakness	289/536 (53.9)	363/1382 (26.3)	<0.001
Dizziness	111/536 (20.7)	240/1382 (17.4)	0.089
Chest pain	166/536 (31.0)	220/1382 (15.9)	<0.001
Echocardiographic data			
LVEF, *n* (%)	488 (90.9)	1045 (75.6)	
LVEF, mean % (SD)	55.9 (11.5)	44.6 (13.9)	<0.001
Left atrial diameter, *n* (%)	455 (84.7)	1202 (87.0)	
Left atrial diameter, mean mm (SD)	45.1 (6.9)	46.9 (8.9)	0.011

AF, atrial fibrillation; AFA, Atrial Fibrillation Ablation Long-Term Registry; AFG, Atrial Fibrillation General Pilot Registry; COPD, chronic obstructive pulmonary disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; EHRA, European Heart Rhythm Association; LVEF, left ventricular ejection fraction; PM, pacemaker; SD, standard deviation; TIA, transient ischaemic attack.

Pier Luigi Temporelli[1], Roland R. Tilz[2], Elena Arbelo[3,4,5], Nikolaos Dagres[6], Cécile Laroche[7], Harry J. Crijns[8], Carina Blomstrom-Lundqvist[9], Paulus Kirchhof[10,11], Gregory Y.H. Lip[12,13], Giuseppe Boriani[14], Evengy Pokushalov[15], Eleni Nakou[16], Josep Brugada[3], and Luigi Tavazzi[17]*

[1]Division of Cardiology, Istituti Clinici Scientifici Maugeri, IRCCS, Veruno (NO), Italy; [2]Department of Cardiology, Angiology and Intensive Care Medicine, University Heart Center Luebeck, Medical Clinic II, University Hospital Schleswig-Holstein, Luebeck, Germany; [3]Department of Cardiology, Cardiovascular Institute, Hospital Clinic de Barcelona, Universitat de Barcelona, Barcelona, Spain; [4]Institut d'Investigació August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [5]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; [6]Department of Electrophysiology, Heart Center Leipzig, Leipzig, Germany; [7]EURObservational Research Programme (EORP), European Society of Cardiology, Sophia Antipolis, France; [8]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands; [9]Department of Medical Science and Cardiology, Uppsala University I, Uppsala, Sweden; [10]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK; [11]Departments of Cardiology, Sandwell and West Birmingham Hospitals NHS Trust and University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [12]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; [13]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [14]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [15]E. Meshalkin National Medical Research Center of the Ministry of Health of the Russian Federation, Novosibirsk, Russia; [16]Barts Heart Centre, St Bartholomew's Hospital, London, UK; and [17]Maria Cecilia Hospital, GVM Care & Research, Cotignola (RA), Italy

*Email: direzionescientifica-mch@gvmnet.it

References

1. Kirchhof P, Benussi S, Kotecha D, Casadei B, Ahlsson A, Atar D, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren Bogdan J, Popescu A, Schotten U, Van Putte B, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
2. Turagam MK, Garg J, Whang W, Sartori S, Koruth JS, Mille MA , Langan N, Sofi QA, Gomes A, Choudry S, Dukkipat SR, Reddy VY. Catheter ablation of atrial fibrillation in patients with heart failure: a meta-analysis of randomized controlled trials. *Ann Intern Med* 2018 Dec 25. https://doi.org/10.7326/M18-0992 [Epub ahead of print].
3. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D; CASTLE-AF Investigators Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427.
4. Tofield A. The CABANA trial: a first glance at an important study. *Eur Heart J* 2018;**39**:2767–2779.
5. Arbelo E, Brugada J, Blomström-Lundqvist C, Laroche C, Kautzner J, Pokushalov E, Raatikainen P, Efremidis M, Hindricks G, Barrera A, Maggioni A, Tavazzi L, Dagres N; ESC-EHRA Atrial Fibrillation Ablation Long-term Registry Investigators Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry. *Eur Heart J* 2017;**38**:1303–1316.
6. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, Oliveira MM, Mairesse G, Crijns HJ, Simantirakis E, Atar D, Kirchhof P, Vardas P, Tavazzi L, Maggioni AP. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace* 2014;**16**:308–319.
7. Kheirckhahan M, Marrouche NF. It's time for catheter ablation to be considered as first time treatment option in patients with atrial fibrillation and heart failure. *Heart Rhythm* 2018;**15**:658–659.
8. Packer M, Kowey PR. Building castles in the sky: catheter ablation in patients with atrial fibrillation and chronic heart failure. *Circulation* 2018;**138**:751–753.