Predictors of Improvement in Left Ventricular Systolic Dysfunction in Patients with Atrial Fibrillation Undergoing Catheter Ablation: Systematic Review

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Abstract

Background: Left ventricular systolic dysfunction (LVSD) can improve after catheter ablation (CA) in many patients with AF. However, prospective prediction of response can be challenging. The aim of this study was, therefore, to perform a systematic literature review of features associated with improvement in left ventricular ejection fraction (LVEF) in patients with AF and LVSD undergoing first CA. **Method:** Systematic search of Ovid MEDLINE, Embase and Cochrane Library databases up to 24 January 2024, for studies involving adult patients with LVSD receiving treatment for AF. The focus was on research articles and clinical trials reporting features associated with changes in LVEF following CA. The review followed PRISMA guidelines. **Results:** A total of 789 unique articles were reviewed and 20 were included in the systematic review. Sixty-nine per cent (range, 54–79%) of included patients met the criteria for responder status, which were based on LVEF improvement (usually an increase in LVEF >10% or to >50% at follow-up). Baseline surrogates of myocardial fibrosis on MRI (R^2=–0.67), electroanatomical mapping (R^2=–0.93) and biochemical surrogates have shown the strongest association with LVEF change. Left atrium and LV chamber size, diastolic dysfunction ECG-based parameters and a known heart failure aetiology have shown prognostic value independently and in combination. **Discussion:** Imaging, clinical and ECG-based surrogates of LV fibrosis may be pre-CA markers of LVEF improvement in patients with AF and LVSD. However, the confounding effect of procedural outcomes should be considered. A composite risk stratification tool would have clinical utility in risk stratification and patient selection; however, prospective studies are needed.

Keywords

AF, catheter ablation, heart failure, left ventricular systolic dysfunction

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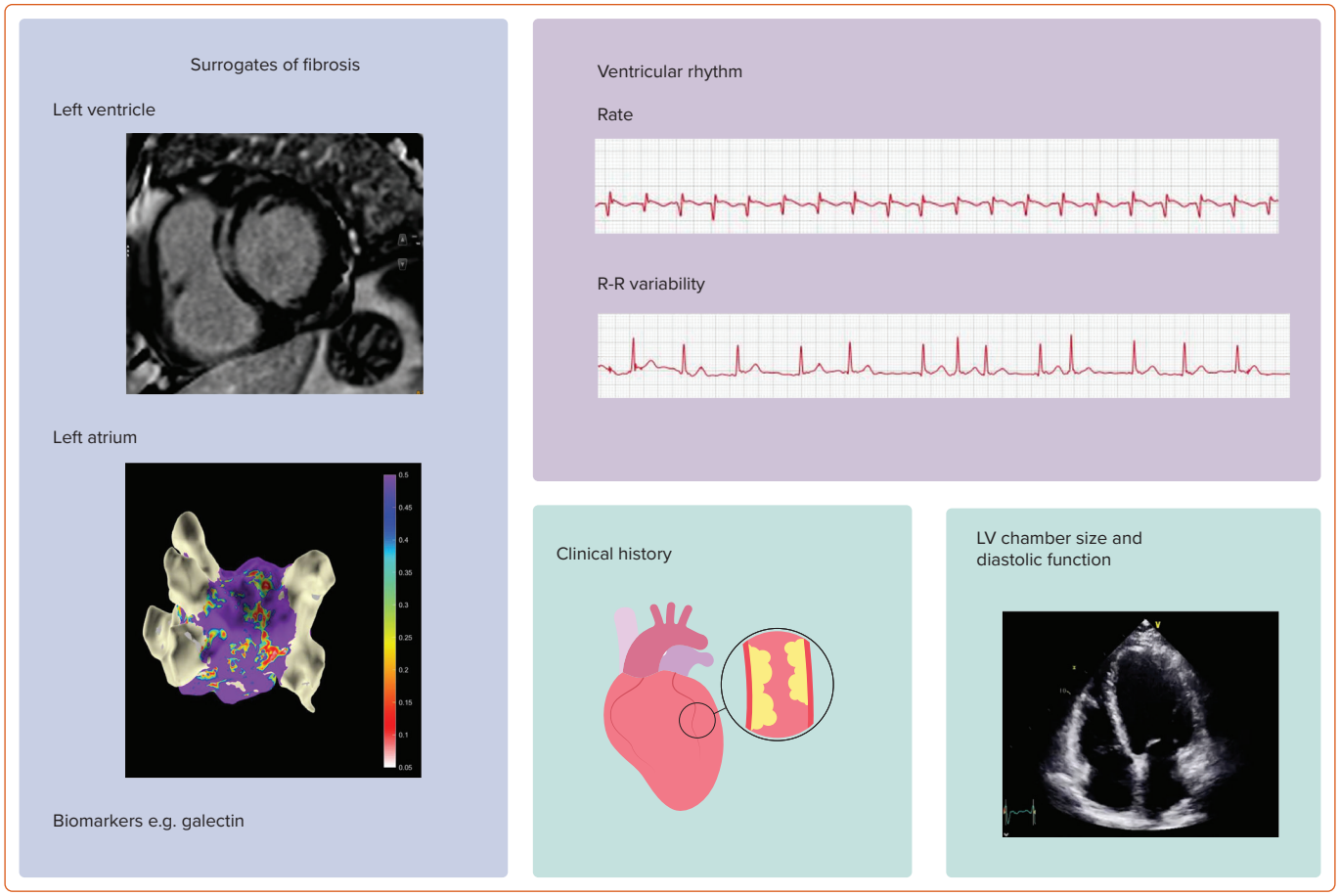
Heart failure (HF) has a prevalence of 1–2% in adults and accounts for 5% of emergency hospital admissions.[1,2] AF co-exists with HF with reduced ejection fraction (HFrEF) in up to 40% of patients and is associated with worse outcomes and reduced therapeutic effects from medical and cardiac resynchronisation therapy.[1]

Catheter ablation (CA) of AF has been shown to induce reverse remodelling in patients with HFrEF, which can lead to improvement of left ventricular (LV) function with associated improvement in HF outcomes, hospitalisation risk and, potentially, cardiovascular death.[3–6] However, this benefit is not uniformly distributed. The mean improvement in LV ejection fraction (LVEF) demonstrated in randomised controlled trials of CA shows a wide standard deviation of the quantitative outcome; suggesting that although most patients have improved LVEF after CA, some patients experience less or no improvement. Guidelines recommend CA as first-line therapy if a reasonable expectation of improvement is suspected.[7] However, predicting response is challenging with no proven method for stratification.

Patients with AF-mediated left ventricular systolic dysfunction (LVSD) may be reasonably expected to have reverse remodelling after the restoration of sustained sinus rhythm. However, patients with bystander AF, in whom the LVSD is caused by an alternative driver, may not have improved LVEF and thus may not derive benefit. Based on this response to CA, patients can be retrospectively classified as 'responders' or 'non-responders', respectively.

Contemporary guidelines provide a class 2b indication for AF ablation in patients in whom AF is suspected to contribute to HF development.[8] However, prospectively attributing HFrEF causatively to AF may only be possible retrospectively.

Central Illustration: Features Associated with Improvement in Patients with Left Ventricular Systolic Dysfunction Undergoing Catheter Ablation



Rationale

Several existing studies have attempted to identify baseline features that can be used to prospectively stratify HFrEF patients before they undergo CA of AF. However, no feature or collection of features has been accepted or adopted to support patient selection.[8,9] A risk stratification tool could support physician decision-making when considering referral for CA or repeated CA attempts while also helping prevent potential non-responders from undergoing unnecessary invasive procedures. The rationale for this systematic review was to collate the existing data and evaluate the potential features that may be included in such a tool.

Objectives

To systematically review the literature to identify features that are associated with improvement in LVSD following CA in patients with AF.

Methods

We followed the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist.[10,11] The systematic review was prospectively registered (PROSPERO registration CRD42024504756).

PICO Framework

- Population: adult patients with a diagnosis of LVSD (LVEF <50%) undergoing CA for AF.
- Index model/predictor: any predictor of improvement in cardiac function after CA in the population.
- Comparators: other predictors or prediction models.
- Outcomes: any measure of LVEF change; the presence of response criteria to the intervention.

Study Selection

Searches were undertaken across three medical databases: Ovid MEDLINE (via PubMed), Embase and Cochrane Library. The search was performed from 1998 (the first publication of pulmonary vein isolation for AF) until 23 January 2024. Search terms are listed in *Supplementary Table 1*.

A systematic approach was used to manage records and data throughout the review using reference management software (Papers, ReadCube; https://www.papersapp.com/). All search results were imported, and duplicates were removed before screening.

Selection process: all titles and/or abstracts of the retrieved articles were screened by two independent reviewers (NA and AH) with the inclusion of equivocal articles determined through discussion with a third reviewer (RJS). Articles that met the preliminary criteria were then assessed in full to determine their eligibility for inclusion. All references of reviewed full texts were also considered for inclusion.

Eligibility Criteria

Studies were considered eligible for inclusion if they:

- were original research articles or clinical trials;
- focused on patients undergoing their first AF CA procedure at the time of enrolment (repeat procedures during the study duration were allowed);

- focused on adult patients diagnosed with AF and LVSD;
- reported on the change in LVEF from before versus after CA as an endpoint, given as either a continuous or categorical variable; and
- were published in English.

Studies were excluded if they were reviews, commentaries, editorials, or case reports. They were excluded if they enrolled the population of interest as part of a mixed cohort (e.g. a combined cohort of HF patients with and without reduced EF) without reported subgroup analysis, or if the change in LVEF was reported as part of a composite endpoint only.

The predictive features that were reported in the included studies were categorised into groups based on acquisition modality, for example, imaging-based investigations or ECG-derived data. Any discrepancies in data extraction were discussed and resolved to ensure accuracy. Study methods followed the PRISMA guidelines.

Data and Variables Extracted

Trial design and pertinent definitions (LVEF threshold for inclusion and responder criteria) were recorded for each study. Demographics, the prevalence of responders and follow-up duration were extracted. Variables analysed for regression analysis (univariable and multivariable) were recorded, including the methodology of measurement. Whether the feature was evaluated as a continuous, discrete or ordinal variable was also extracted.

The odds ratio of a considered variable associated with responders versus non-responders was collected and expressed as an OR with 95% CI and associated p-value. Risk prediction using the area under the receiver operating characteristic curve (AUROC) was also included when reported. A sensitivity analysis limited to prospective studies will also be reported.

Results

Our initial search strategy yielded a total of 789 articles across the selected databases (*Figure 1*). After the removal of duplicates, a total of 444 unique records were screened. A total of 56 studies were included for review of the full manuscript.

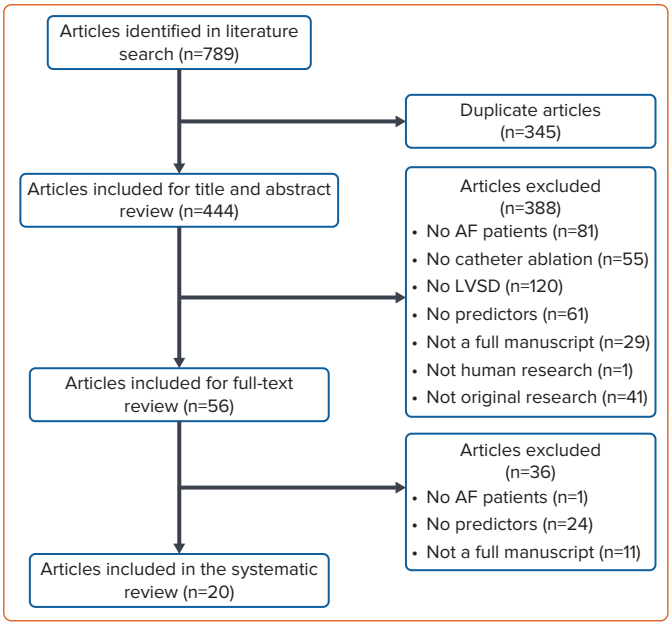
Twenty studies were included, comprising a total of 2,089 unique patients. A total of 67.8% were women (range, 61–100%), and the mean age ranged from 59 ± 11 years to 69.1 ± 8.8 years. A detailed description of study baseline characteristics is presented in *Table 1*. The definition of LVSD for inclusion was similar across the included studies, with the upper threshold between 40% and 50% (*Table 2*). There were differences in the definition of response to CA (*Table 2*). Three out of 20 included trials defined responders according to the universal definition criteria for HF with improved EF published in 2021.[12–14] Patients with a baseline LVEF ≤40% required a ≥10% point increase whereas patients with LVEF 41–49% required improvement to ≥50%. Echocardiography was used for LVEF quantification in all studies except the CAMERA-MRI trial.[15] The timepoint of follow-up imaging also varied, with most studies doing so between 3 months and 12 months after CA. In total, 1,380 participants (69%) were classified as responders to CA based on individual study criteria. This ranged from 54% to 79% (*Table 2*).

Imaging-based Features for Catheter Ablation Response

Systolic Function

Baseline LVEF was evaluated for association with response in five studies.[13,16–19] There was no significant association on multivariable modelling when analysed as a continuous variable. Yu et al. reported that patients with LVEF <40% had a greater likelihood of response than patients with LVEF 40–49% (OR 4.03; 95% CI [1.41–11.53]; p<0.01).[17]

Figure 1: Study Selection



LVSD = left ventricular systolic dysfunction.

Diastolic Function

Two studies evaluated the association of echocardiographic parameters of diastolic function with response. Yang et al. showed that the E/e' ratio was associated with non-response (OR 1.13; 95% CI [1.03–1.24]; p=0.01) and that an E/e' ratio >15 had an AUROC of 0.704 (p<0.001) for non-response.[13] Morishita et al. demonstrated an association with septal e' and non-response that was independent of E_{max} (OR 1.8; 95% CI [1.1–2.7]; p=0.014).[20]

Chamber Dimensions

Left Ventricular Chamber Size

The baseline LV diameter at end-diastole (LVEDD) on pre-ablation echocardiography was the most frequently analysed parameter, evaluated in six studies of 481 unique patients.[17,20–24] Responders had significantly shorter LVEDD at baseline. It was inversely associated with response when assessed as a continuous variable on multivariable regression analysis in two studies (OR 0.85; 95% CI [0.75–0.95]; p=0.005; and OR 0.86; 95% CI [0.78–0.96]; p=0.005).[20,24] As a discrete variable, LVEDD <53 mm had an OR of 2.58 (95% CI [1.29–6.12]; p=0.021) for response and AUROC of 0.762.[21]

LV volume on echocardiography was also evaluated in three further studies.[16,19,25] Although responders had smaller LV volumes, as a continuous variable it was not associated with response on multivariable analysis. Yazaki et al. evaluated indexed LV end-systolic volume ≤49.8 ml/m^2 as a discrete variable and demonstrated a significant association with response (OR 2.18; 95% CI [1.22–4.13]; p=0.01; AUROC=0.751).[19]

Indexed Left Atrial Volume

In the ANTWOORD study, baseline-indexed left atrial volume (LAVi) as a continuous variable was associated with a significantly lower likelihood of responder status after CA on multivariable regression (OR 0.92; 95% CI [0.87–0.98]; p=0.002).[16] LAVi <50 ml/m^2 as a discrete variable was also an

Table 1: Patient Demographics and Rate of AF Recurrence after Catheter Ablation

Study	Cohort Size	Cohort Type	Cohort Age (Years)	Male	Hypertension	Diabetes	Persistent AF	CHADSVASc Score	BNP (pg/ml)	AF Recurrence/Rhythm at Follow-up Imaging
Azuma et al. 2021[27]	32	NICM only*	67 ± 9	29 (91)	19 (59)	(16)	32 (100)	2.5 ± 0.9	240 ± 188	100% in sinus rhythm at follow-up imaging
Bergonti et al. 2023[12]	605	Any LVSD	61 ± 9	461 (76)	357 (59)	107 (18)	483 (80)	–	–	Any AF or AT: 118/385 (30.6%) versus 86/167 (51.5%), permanent AF 12/340 (3.5%) versus 19/152 (12.5%)
Bergonti et al. 2022[16]	111	Any LVSD	61 ± 10	68 (61)	46 (41)	15 (14)	91 (82)	2.3 ± 1.4	–	Any AF/AT: 46 (41%), permanent AF 9 (8%); all non-responders
Kirstein et al. 2020[14]	103	Any LVSD	64 [17]	71 (69)	71 (69)	35 (30)	483 (80)	3 [2]	–	87 (85%) free from recurrence, 100% in sinus rhythm or A-paced at follow-up imaging
Koene et al. 2019[29]	52	Any LVSD	63 ± 8	52 (100)	(83)	(12)	(60)	2.6 ± 1.0	-	26 (50%) free from AF recurrence
Nomura et al. 2022[30]	51	NICM only	64 [17]	43 (86)	18 (35)	5 (10)	79 (78)	2 [2]	781 [1,429]	7/63 (11%) had AF recurrence and were excluded from the study results
Prabhu et al. 2017[15]	33	NICM only*	59 ± 11	31 (94)	39 (13)	12 (4)	33 (100)	2.4 ± 0.9	266 ± 210	Any AF/AT: 75%. A total of 100% in sinus rhythm at follow-up imaging
Prabhu et al. 2016[34]	101	Any LVSD*	55 ± 11 versus 61 ± 7	89 (88.1)	51 (50)	51 (50)	79 (78)	–	–	Any AF/AT: 24 (25%)
Ukita et al. 2021[21]	81	Any LVSD	64 ± 10 versus 64 ± 9	53 (65)	33 (41)	17 (21)	81 (100)	–	–	Any AF/AT: responder: 7/48 (15%) versus non-responder: 12/33 (36%). A total of 100% in sinus rhythm at follow-up imaging
Yang et al. 2022[13]	156	Any LVSD	64 ± 11	105 (67)	73 (47)	28 (18)	102 (65)	2.5 ± 1.3 versus 2.3 ± 1.3	640 ± 935	78% in sinus rhythm at follow-up imaging
Yu et al. 2022[17]	120	NICM only§	64 ± 10	83 (69)	54 (45)	11 (9)	120 (100)	2.5 (3)	1,335 (1,949)	Any AF/AT: 23% at 12 months
Aoyama et al. 2023[22]	60	Any LVSD	69 ± 9	45 (75)	30 (50)	13 (22)	42 (70)	3.0 ± 1.3	160.7 [258]	Any AF/AT: 10/60 (17%) at follow-up
Aoyama et al. 2020[32]	34†	Any LVSD	70 ± 11 versus 65 ± 11	32 (80)	19/40 (48)	14/40 (35)	–	–	260 ± 193 versus 132 ± 107	Any AF/AT: 8/40 (20%) at follow-up
Aoyama et al. 2024[23]	97	NICM only	67 ± 11	74 (73)	49 (51)	22 (23)	70 (73)	3.1 ± 1.6	148.7 (177)	Any AF/AT: 23/97 (24%) at follow-up
Nishikawa et al. 2023[25]	33	Any LVSD	66 ± 10 versus 68 ± 9	20 (61)	21 (64)	7 (21)	29 (88)	3.4 ± 1.4 versus 3.6 ± 1.8	844 ± 663 versus 3,183 ± 2,167	Any AF/AT: 4/33 (12%) at follow-up
Clementy et al. 2018[18]	75	Any LVSD	63 ± 10	61 (81)	42 (56)	19 (25)	75 (100)	3.0 ± 1.3	445 ± 650	Persistent AF: 16/75 (21%) at 6 months
Ichijo et al. 2018[24]	51‡	Any LVSD	60 ± 11	41 (80.3)	23 (45)	8 (16)	39 (77)	–	1,258 ± 1,017	Any AF/AT: 3/51 (6%) at follow-up
Morishita et al. 2023[20]	72	NICM only*	63 ± 11	59 (81.9)	32 (44)	14 (19)	72 (100)	–	5,618 ± 23,058	0§
Takahashi et al. 2023[28]	82	NICM only	63 ± 11 versus 67 ± 10	72 (85)	39 (46)	16 (19)	82 (100)	–	504 ± 375 versus 953 ± 1,439	100% in sinus rhythm at follow-up imaging
Yazaki et al. 2020[19]	140	Any LVSD	60 ± 10	118 (84)	61 (44)	23 (16)	84 (60)	–	–	Any AF/AT: responders: 35/97 (36%) versus non-responders: 25/43 (58%) p=0.02. Persistent AF: Responders: 6/97 (7%) versus non-responders: 8/43 (20%) p=0.06

*Continuous and ordinal variables are reported as mean ± SD or median [IQR]. Where reported as stratified groups based on response, both values are given as responder versus non-responder. Categorical variables are reported as n (%). *Patients with cardiac implantable electronic device were excluded. †40 patients in total; 34 patients had AF, and six had atrial flutter only. Results are reported for the AF subgroup. ‡106 patients in total; 51 included patients with heart failure with reduced ejection fraction, with results reported for this sub-group. §Patients with dilated cardiomyopathy were excluded. AT = atrial tachycardia; BNP = brain natriuretic peptide; NICM = non-ischaemic cardiomyopathy; LVSD = left ventricular systolic dysfunction.*

Table 2: Defining Criteria for Left Ventricular Systolic Dysfunction and Response

Study	Imaging Modality	Upper LVEF Threshold for LVSD Inclusion (%)	Response Criteria (LVEF), %	Proportion Meeting Responder Criteria, n (%)
Azuma et al. 2021[27]	TTE	50	+10	21 (65)
Bergonti et al. 2023[12]	TTE	50	+10	60 (54)
Bergonti et al. 2022[16]	TTE	50	+10 or >50	427 (70)
Kirstein et al. 2020[14]	TTE	40	+10 or >50	76 (74)*
Koene et al. 2019[29]	TTE	50	+7.5	30 (58)
Nomura et al. 2022[30]	TTE	45	>50	37 (73)
Prabhu et al. 2017[15]	MRI	50	>50	19 (58)
Prabhu et al. 2016[34]	TTE	50	+15	–
Ukita et al. 2021[21]	TTE	50	+10	48 (59)
Yang et al. 2022[13]	TTE	50*	+10 or >50	113 (72)
Yu et al. 2022[17]	TTE	50	+20 or >55	87 (73)
Aoyama et al. 2023[22]	TTE	50	>50	43 (72)
Aoyama et al. 2020[32]	TTE	50	>50	30 (75)
Aoyama et al. 2024[23]	TTE	50	+20 or >50	67 (69.8)
Nishikawa et al. 2023[25]	TTE	50	>50	24 (73)
Clementy et al. 2018[18]	TTE	40	>50	50 (67)
Ichijo et al. 2018[24]	TTE	45	>50	37 (72.5)
Morishita et al. 2023[20]	TTE	45	+15 or +10 if >50	57 (79)
Takahashi et al. 2023[28]	TTE	40	50	57 (67)
Yazaki et al. 2020[19]	TTE	50	+20 or >50	97 (69)

LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic function; TTE = trans-thoracic echocardiography.

independent predictor of responder status (OR 9.1; 95% CI [1.8–47.9]; p<0.001). AF recurrence rate was similar between responders and non-responders (HR 0.71; 95% CI [0.40–1.28]; p=0.25). However, the rate of persistent AF recurrence was different between responders and non-responders (0 versus 18%; p<0.01). LAVi was not significantly associated with response when analysed by Yazaki et al. The rate of AF recurrence was higher and significantly different between responders and non-responders (35% versus 58%; p=0.02).[19]

Late Gadolinium Enhancement

Late gadolinium enhancement (LGE) on MRI has been associated with regions of fibrosis.[26] In the CAMERA-MRI study, the prognostic value of LGE on LVEF was a pre-specified secondary endpoint and was reported separately for each arm of the study. Patients undergoing CA were dichotomised based on the absence (<1% LGE burden) or presence of LGE in the LV myocardium. LGE-negative status was associated with greater improvement in LVEF compared with LGE-positive status (22.3% versus 11.6%; p=0.007). LGE-negative patients were more likely to achieve normalisation of their LV function (73% versus 21%; p=0.009). LGE-negative status was a predictor of LVEF normalisation (p=0.034). There was also an inverse correlation between LGE burden as a continuous variable and LVEF change (r=−0.67, p=0.009)

T1 Mapping

T1 mapping evaluates myocardial tissue composition by quantifying the extracellular volume (ECV) fraction on MRI.[24] Azuma et al. showed that patients with low ECV (<28%) had a significantly greater improvement in LVEF than patients with high ECV (23.7 ± 10.9% versus 7.9 ± 9.2%; p<0.001).[27] However, the combination of T1 mapping and LGE burden was not associated with greater discrimination than LGE alone for identifying responders to CA (AUROC 0.830; 95% CI [0.63–1.00] versus AUROC 0.602; 95% CI [0.37–0.84]; p=0.35).

Left Atrial Low-voltage Zones

In the Fibrosis-HF study, left atrial low-voltage zones (LVZ) were detected in 39/103 patients (38%) undergoing first-time CA.[14] A strong inverse correlation was shown between the LVZ burden and responder status (R^2=0.931) and was an independent predictor of non-response on multivariable regression analysis (OR 7.2; 95% CI [2.2–23.4]; p=0.001). No patient with >35% LVZ burden responded to CA.

ECG-based Parameters

Heart Rate

Resting heart rate was evaluated in four studies.[17,22,23,28] The recording duration and setting differed between groups (*Supplementary Material Table 2*). It was only shown to be significantly associated with response in one study by Yu et al., in which an averaged heart rate <80 BPM from three pre-ablation ECGs was associated with response (OR 5.38; 95% CI [1.64–17.58]; p<0.01).[17]

R-R Variability

Koene et al. reported greater R-R interval dispersion on pre-ablation ECG in responders (645 ± 155 ms versus 537 ± 154 ms, p=0.02).[29] On multivariable regression it was the only significant predictor of response after adjustment for echocardiographic and ECG-based variables (OR 1.59; 95% CI [1.00–2.55]; p=0.03).

QRS Morphology

QRS width, as a continuous variable, was inversely associated with response in the ANTWOORD study (OR 0.93; 95% CI [0.89–0.96];

Table 3: Predictive Accuracy of Discrete Markers

Study	Marker Type	Marker (Discrete)	AUROC
Takahashi et al. 2023[28]	Angiography	Coronary blood flow	0.87 (95% CI [0.83–0.92]) at frame count <35
Aoyama et al. 2023[22]	Biomarker	TnI	0.82 at TnI <11.1 pg/ml
Clementy et al. 2018[18]	Biomarker	Galectin-3	0.72 at galectin-3 ≤26 ng/ml
Nishikawa et al. 2023[25]	CT	ECV fraction	0.9583 at ECV fraction <37.7%
Nomura et al. 2022[30]	ECG	S-QRS score	0.76 at S-QRS <2
Ichijo et al. 2018[24]	TTE	LVEDD	0.77 at LVEDD <53.5 mm
Morishita et al. 2023[20]	TTE	LVEDD	0.74 at LVEDD <53 mm
Morishita et al. 2023[20]	TTE	Septal e'	0.745 at e' >6.3 cm/s
Yazaki et al. 2020[19]	TTE	Septal e'	0.753 at e' >6.3 cm/s
Yazaki et al. 2020[19]	TTE	LVESVi	0.751 at LVESVi <49.8

AUROC = area under the receiver operating characteristic curve; ECV = extracellular volume; LVEDD = left ventricular end-diastolic diameter; LVESVi = indexed left ventricular end-systolic volume; S-QRS = Selvester-QRS; TnI = troponin I; TTE = trans-thoracic echocardiography.

p<0.001).[16] QRS<120 ms, as a dichotomous variable, was associated with response (OR 19.0; 95% CI [4.1–88.4]; p<0.001).

Nomura et al. evaluated the Selvester QRS (S-QRS) score on the sinus rhythm ECG recorded 48 hours after CA.[30] The ordinal variable was associated with a greater likelihood of response (OR 2.07; 95% CI [1.19–4.00]; p<0.01) and an S-QRS score <2 points had an AUROC of 0.79 in predicting LVEF normalisation.[31]

Biomarkers

Brain Natriuretic Peptide

Baseline serum brain natriuretic peptide (BNP) or N-terminal-proBNP (NT-proBNP) levels were evaluated in four studies.[18,25,32,33] Although levels were lower in responders, no study showed an independent association with response on multivariable regression.

Troponin

Lower preprocedural high-sensitivity troponin (hsTn)T was associated with response in two sequential studies by the same group.[22,32] A baseline hsTnI <11.1 pg/ml achieved an AUROC of 0.82 (p<0.001) and hsTnT <12 pg/ml achieved an AUROC of 0.83 (p=0.004).

Galectin-3

Galectin-3, a proposed biomarker of myocardial fibrosis, and AF onset, was shown to be lower in responders (17.9 ± 5.2 ng/ml versus 28.4 ± 18.4 ng/ml) and a serum level ≥26 ng/ml achieved an AUROC of 0.72 (p<0.0001; *Table 3*).[18]

Coronary Blood Flow

One study has reported an association between the rate of coronary opacification on invasive angiography in patients with non-ischaemic cardiomyopathy and the likelihood of subsequent response to CA. The rate of blood flow was slower in responders in each major coronary vessel and the total frame count required to visualise opacification was associated with response (OR 1.38; 95% CI [1.14–1.67]; p<0.001; *Table 3*).

Clinical Features

Demographics

A significant association between age and response was reported in one study.[22] Aoyama et al. reported that responders were younger, and age was inversely associated with response (OR 0.91; 95% CI [0.82–1.00]; p<0.04). Anthropometric measurements were evaluated in three studies.[18,22,23] Although no significant association was seen with height or weight, BMI was associated with response on multivariable regression analysis (OR 1.13; 95% CI [1.01–1.31]; p=0.04).

History of Aetiology

Five studies have evaluated a known HF aetiology with likelihood of response to CA, although its definition varied between studies (*Supplementary Material Table 2*).[13,16,19,24,34] Patients with ischaemic cardiomyopathy were excluded from several studies (*Table 1*).

Prabhu et al. showed that patients with a previous MI, cardiomyopathy or valvular disease did not have significant improvement in LVEF (35 ± 8% to 38 ± 10%, p=0.25) whereas patients with no known diagnosis did (36 ± 8% to 50 ± 11%, p<0.001).[34]

Clementy et al. reported that a history of ischaemic heart disease was also independently associated with a lower likelihood of response (OR 0.14; 95% CI [0.03–0.60]; p=0.008).[18] The absence of a known HF aetiology had the greatest odds ratio of association with response in the multivariable regression model in the ANTWOORD study (OR 33.5; 95% CI [6.0–187.4]; p<0.001).[16]

Atrial Fibrillation Burden

In the ANTWOORD study, patients with persistent rather than paroxysmal AF were more likely to be responders to CA (OR 17.8; 95% CI [1.40–217.9]; p=0.03).[16] However, the change in AF burden at baseline or follow-up was not reported.

Prospective Studies

Sensitivity analysis limited to prospective trials included four studies (*Table 4*). Fibrosis-HF and CAMERA-MRI reported significant association between imaging-based parameters of left atrium (LA) and LV fibrosis, respectively, and LVEF response.[14,15] Both studies also reported significant correlation with the change in absolute LVEF (*Table 5*). Clementy et al. evaluated the relationship with galectin-3 and Nomura et al. prospectively studied the association with Selvester score on ECG.[18,35] The two studies reported AUROCs of 0.72 and 0.76, respectively, for identifying LVEF response to CA.

Combined Scores

Two studies evaluated the combined value of different parameters.[12,25] Four parameters derived from the ANTWOORD study were weighted according to the strength of their association and validated as a combined risk stratification tool in a multicentre study (QRS >120 ms [2 points], known HF aetiology [2 points], paroxysmal AF [1 point], LAVi >50 ml/m^2 [1 point]). The absolute duration of HF and onset relative to AF were significant features on univariable analysis but not in their multivariable model. Of the 605 patients from eight centres, 427 (70.0%) were responders; a significantly higher proportion than in the ANTWOORD study (54.1%, p<0.001). A score <2 was associated with a 93% probability of response, whereas 24% of patients with a score >3 achieved responder status, producing a c-statistic of 0.86 in the external validation cohort. The prevalence of any AF or atrial tachycardia recurrence (30.6% versus 51.5%, p<0.001) and persistent AF recurrence (9.6% versus 34.1%, p<0.001)

Table 4: Study Design

Study	Retrospective Versus Prospective	Centre Type	Trial Design	Follow-up LVEF Assessment (Months After CA)
Azuma et al. 2021[27]	Retrospective	Single-centre	Observational	Mean ± SD: 10.6 ± 10.5*
Bergonti et al. 2023[12]	Retrospective	Multicentre	Observational	12
Bergonti et al. 2022[16]	Retrospective	Single-centre	Observational	Median (IQR): 4.8 (0.6–10.4)
Kirstein et al. 2020[14]	Prospective	Single-centre	Observational	6
Koene et al. 2019[29]	Retrospective	Two-centre	Observational	>1.25
Nomura et al. 2022[30]	Prospective	Single-centre	Observational	12
Prabhu et al. 2017[15]	Prospective	Multicentre	Randomised controlled trial	6
Prabhu et al. 2016[34]	Retrospective	Multicentre	Observational	>6
Ukita et al. 2021[21]	Retrospective	Single-centre	Observational	>6
Yang et al. 2022[13]	Retrospective	Single-centre	Observational	3–12
Yu et al. 2022[17]	Retrospective	Single-centre	Observational	3–12
Aoyama et al. 2023[22]	Retrospective	Single-centre	Observational	>3
Aoyama et al. 2020[32]	Retrospective	Single-centre	Observational	>3
Aoyama et al. 2024[23]	Retrospective	Multicentre	Observational	3–12
Nishikawa et al. 2023[25]	Retrospective	Single-centre	Observational	>3
Clementy et al. 2018[18]	Prospective	Single-centre	Observational	>6
Ichijo et al. 2018[24]	Retrospective	Single-centre	Observational	Mean ± SD: 13.2 ± 10.9
Morishita et al. 2023[20]	Retrospective	Single-centre	Observational	Mean ± SD: 11 ± 2
Takahashi et al. 2023[28]	Retrospective	Single-centre	Observational	>6
Yazaki et al. 2020[19]	Retrospective	Single-centre	Observational	>12

**Duration between baseline and post-CA echocardiography. CA = catheter ablation; LVEF = left ventricular ejection fraction.*

was lower in responders. The risk of HF hospitalisation and mortality was also lower in responders.[12]

Nishikawa et al. evaluated a composite risk stratification tool incorporating serum NT-proBNP, left ventricle end-diastolic volume on echocardiography and ECV on cardiac CT in 33 patients. Each parameter was associated with response on univariate analysis, and when combined, they had an AUROC of 0.9583 (p<0.0001).[25] The rates of AF recurrence were similar between non-responders and responders (13% versus 11%, p=1.0)

Discussion

It is important to identify those patients who are most likely to respond to treatment, particularly when exposing the patient to a potentially risky and uncomfortable procedure such as an AF CA. Patients who respond to CA also have a better prognosis than those who do not.[12,18,23]

The temporal association between AF and HF and the baseline AF burden may be empirically compelling parameters to consider but there is limited evidence to support these because they are relatively difficult to define objectively without implantable devices or screening, and thus difficult to quantitatively evaluate. Of the evaluated pre-procedural parameters, ventricular LGE on MRI seems to have the strongest association with a response after CA. For patients who are unable to access cardiac MRI or in whom it is contraindicated, troponin or galectin-3 may be biochemical surrogates of fibrosis but further study is needed. Having a known HF aetiology may be a demographic surrogate of underlying fibrosis, thus conferring its negative prognostic value. Empirical features may share this mechanistic association and could explain why significant variables were not retained in multivariable models, such as HF duration and known HF aetiology in the ANTWOORD study.

Table 5: Correlation between Continuous Marker and Change in Left Ventricular Ejection Fraction

Study	Marker Type	Marker (Continuous)	Correlation
Azuma et al. 2021[27]	MRI	ECV fraction	−0.47
Prabhu et al. 2017[15]	MRI	LGE	−0.67
Azuma et al. 2021[27]	MRI	LGE	−0.49
Kirstein et al. 2020[14]	EAM	LVZ burden	0.931

EAM = electroanatomical mapping; ECV = extracellular volume; LGE = late gadolinium enhancement; LVZ = left atrial low-voltage zone.

Fibrosis is a hallmark of structural heart disease and typically suggests irreversible remodelling. However, diffuse fibrosis can regress and is associated with LVEF improvement, even in patients with localised fibrosis.[36] LV LGE on MRI may reflect a range of disease processes, from ischaemic damage to arrhythmia-mediated remodelling.[26,37] Qualitative interpretation of the pattern of fibrosis and with clinical correlation may aid interpretation.

The strongest relationship was with LVZ: no improvement was seen in any patients with LVZ burden >35%. Although it is a peri-procedural marker, it could inform the prognosis of a continued rhythm control strategy if AF recurs. The correlation between MRI-determined LA fibrosis and LVZ remains to be proven.[31] LVEF improvement was independent of LA fibrosis on pre-procedural MRI in a DECAAF II sub-study.[38] LVZ burden may imply advanced disease. LA stretch and remodelling may lead to irreversible LVEF reduction and LA involvement akin to progressive myocyte disarray in hypertrophic cardiomyopathy.[39,40]

ECG features of AF, namely the regularity (R-R dispersion) and morphology (QRS duration), were also associated with responder status. Both atrioventricular node ablation with pacing and CA normalise ventricular rate and regularity; the former at the cost of non-physiological ventricular activation. Both have demonstrated LVEF improvement in HF patients with greater improvement seen after CA.[41] However, the APAF-CRT trial showed a mortality benefit after atrioventricular node ablation with cardiac resychronisation therapy pacing in patients with permanent AF with a narrow QRS and HF, which may result in part from absolute rate and rhythm control.[42] How best to regularise the rhythm (CA or pacing) is likely to be a decision best driven by patient factors including the patient's age, the chances of success of CA and patient preference.

Although tachycardia-induced cardiomyopathy is well established, the mechanisms underlying LVSD due to rate-controlled AF are less clear.[43,44] The irregularity of ventricular rhythm may disrupt intracellular calcium handling leading to contractile impairment, and this process may be characterised by R-R variability. AF with a fast ventricular rate has been shown to cause LV fibrosis in animal models, and these features have not been considered in a multivariable model to determine independence.[45]

A meta-analysis of eight randomised controlled trials including 1,390 patients in total demonstrated that AF CA significantly improves HF outcomes in patients with LVSD compared with rate control alone.[46] Two trials showed no improvement in LV function after HFrEF.[47,48] However, all trials showed a variance in reported LVEF change, suggesting that some patients respond to CA and some do not. The variability in the cohort-level outcomes between studies may be a result of differential enrolment across these significant independent variables and freedom from AF at follow-up. The variation in follow-up timepoint between studies would also affect the duration of sinus rhythm and time for reverse remodelling. However, interval studies of cardiac function after CA have not shown any significant change in LVEF on echocardiography between 6 months and 12 months.[5]

Standardisation of terminology is important for comparable evaluation. The universal definition of improved EF helps to quantify and standardise this phenomenon, and identifying the variables associated with response may also help to define enrolment criteria in future research.

In practice, a risk stratification tool would have most value in equivocal cases. Therefore, it is also important to prospectively evaluate any tool in patients not routinely referred for CA who are seen in non-specialist electrophysiology and HF clinics. At present, clinicians will need to continue to consider multiple factors when counselling patients about their treatment, giving priority to those that are most predictive. This should include a surrogate of LV fibrosis, such as LGE burden on cardiac MRI or the presence of other disease processes that can cause HF. In addition, LVEDD on echocardiography and width of the QRS complex on ECG should also be reviewed. Ultimately, the patient's wishes will, of course, be the most important factor to consider.

Limitations

The maintenance of sinus rhythm after CA is an important factor for response and is also associated with prognostic benefit.[49] AF recurrence was more than 50% in the non-responder arms of several included studies.[16,33,50] A per-outcome analysis would help to demonstrate the specific impact of sinus rhythm restoration. Patients who revert to persistent AF by the time of follow-up imaging after DC cardioversion do not show significant improvement in LVEF.[51] In clinical practice, patients with AF recurrence may not undergo follow-up imaging and would have been excluded from retrospective analyses. Feature sensitivity could therefore be over- or underestimated by studies with a low success rate for CA. A low success rate may also be influenced by the selected features (e.g. LA size and LVZ), therefore the interpretation of the results of such studies is complex.[52,53] Although some trials reported the rate of AF recurrence, it is not a binary phenomenon. CASTLE-HTx reported that the prognostic benefit of CA in patients with HFrEF was associated with a reduction in AF burden of 31.4 ± 33.3% at 12 months.[3] Post-hoc analysis of the CASTLE-AF trial identified that the prognostic benefit was associated with a reduction in AF burden <50% at 6 months.[54] AF-mediated LV remodelling is a time-dependent phenomenon, with reverse remodelling seen after the prolonged absence of AF, and future studies of predictors of LVEF improvement should consider the utility of continuous rhythm monitoring to evaluate the relationship as a function of change in AF burden.[55–57]

There are also inherent limitations to a literature review. Reporting bias may occur in the publication of retrospective, observational findings in specific cohorts. The additional variables considered for inclusion in multivariable models were also selectively chosen and reported. The four prospective trials included in the sensitivity analysis reported a significant association between parameters of myocardial fibrosis on imaging, ECG or serum with response to CA (although the CAMERA-MRI and Fibrosis-HF trials were prospective, but identification of significant predictors of LVSD response was not the primary objective of either study).[14,15,18,35]

The intention of evaluating predictive markers is in part to help identify patients with LVSD who may not otherwise be referred for CA. However, all patients were referred for CA by their clinical team, aside from the enrolment criteria of CAMERA-MRI.[15] Therefore, even if the included cohorts are similar, they may not represent the general population of patients with LVSD.

Conclusion

Several studies have demonstrated AF-related and patient-related features that are associated with LVEF improvement after CA. This may also help us to understand how AF mediates LVSD and inform further mechanistic study, which is needed. A combination of these features may be combined to develop a risk stratification score; however, it should relate to patients with the most uncertainty of response to maximise clinical utility. ❑

Clinical Perspective

- While catheter ablation of AF typically leads to improved left ventricular function, non-response is seen in up to one-third of patients with left ventricular systolic dysfunction (LVSD).
- Late gadolinium enhancement on MRI, low-voltage zone burden on electroanatomical mapping and biochemical markers of fibrosis are most strongly associated with non-response.
- Existing combination scores may help to stratify the likelihood of response by identifying features associated with alternative drivers of LVSD. Further characterisation of AF-mediated LVSD may help to rule in responders and strengthen such scores.

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