Atrial fibrillation in heart failure: Prime time for ablation!

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Among heart failure (HF) patients, the onset of atrial fibrillation (AF) is often associated with a marked worsening of HF symptoms and increased morbidity and mortality. Among AF patients, 30%–40% experience at least 1 HF episode. New data suggest that, in HF patients, AF rhythm control is superior to rate control and that rhythm control by catheter ablation is superior to antiarrhythmic drugs. In recent years, several trials that addressed the impact of AF ablation on morbidity and mortality included HF patients; however, studies also have specifically investigated the growing cohort of patients suffering from both HF and AF. Although the majority of these trials showed a marked benefit of AF ablation, there are hints that not all HF patients benefit equally from AF ablation. AF treatment in HF is challenging because the same cardiac morbidities that lead to HF can also act as risk factors for the development of the arrhythmogenic substrate that causes AF. In many patients, this arrhythmogenic substrate can be successfully treated by antral pulmonary vein isolation pulmonary vein isolation (PVI). However, due to advanced atrial disease, some patients also might require multiple procedures and/or "PVI plus" ablation strategies. In this review, we summarize current data on the effect of AF ablation in HF patients, with a special focus on the beneficial effect of AF ablation in different clinical HF subgroups.

KEY WORDS Atrial fibrillation; Catheter ablation; Heart failure; Heart failure with preserved ejection fraction; Heart failure with reduced ejection fraction; Invasive treatment; Mortality and morbidity; Vicious circle

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Atrial fibrillation and heart failure—A vicious circle

Heart failure (HF) and atrial fibrillation (AF) both have a wide impact on mortality, hospitalization, stroke risk, and quality of life (QoL) in patients with one of these conditions. If both HF and AF coexist, the risk of developing one of them not only is the summation of each individual disease but increases exponentially, with a major increase in hospitalizations and a 2–3 times higher mortality.[1–3] The Framingham study demonstrated that patients with one of the conditions are prone to experience the other, with an estimated 40% of HF patients developing AF and almost 35% of AF patients experiencing at least 1 episode of HF.[3]

The most important reason for this interlacing of diseases is that—from a pathophysiological standpoint—"AF begets HF" and vice versa. HF is often associated with congestion of the heart chambers with consecutive dilation (of atria), stretch, and fibrosis, but it also causes changes on the neurohumoral as well as cellular levels, which ultimately result in electrical instability (Figure 1). AF can promote HF as a result of the rapid and irregular heart rate and the lack of atrial systole (and thus only passive ventricular filling), which in turn might lead to congestion, heart chamber dilation, fibrosis, and similar neurohumoral changes.[4]

Rate or rhythm control—Early results

The AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial showed that if only antiarrhythmic drugs (AADs) were used, rate control equaled rhythm control in longer-term follow-up (FU) with regard to hard outcomes such as mortality and stroke. However, it soon became clear that the outcomes in the rhythm control arm were significantly negatively impacted by AAD side effects. Moreover, in the rhythm control arm the sinus rhythm (SR) rate (provided by AAD) was quite low and the stroke rate was excessively high, mostly due to (inadequate) termination of oral anticoagulation.[5] These results triggered an interest in rhythm control *by AF ablation,* analyzing the safety and feasibility of AF ablation in HF patients.

The first observational report published in 2006 showed in patients with concomitant AF and heart failure with reduced ejection fraction (HFrEF) a benefit of (successful) AF ablation with regard to left ventricular ejection fraction (LVEF), peak O_2 consumption, and occurrence of decompensated HF, but also improvement of QoL.[6]

AF ablation in HFrEF

After this first encouraging report, several (smaller) randomized controlled trials (RCTs) compared rhythm control

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KEY FINDINGS

- Heart failure (HF) and atrial fibrillation (AF) share common risk factors, and both have a negative impact on morbidity and mortality of cardiovascular patients.
- HF and AF form a vicious circle, promoting by multiple pathways the occurrence of each other and increasing exponentially cardiovascular morbidity and mortality in patients with both conditions.
- In HF patients, rhythm control of AF has been shown to be superior to rate control with regard to hard endpoints such as mortality, morbidity, and worsening of HF symptoms.
- For AF rhythm control, catheter ablation has been proven to be superior to antiarrhythmic medication.
- In HF patients, AF ablation should be regarded as the primary therapeutic option.

provided by catheter ablation to medical treatment (mostly with rate control) in patients with AF and HF (Table 1).[4,7–9]

These trials included mostly patients with persistent AF and HFrEF, and the ablation strategy comprised strategies such as left atrial (LA) lines or complex fractionated atrial electrogram (CFAE) ablation in addition to antral pulmonary vein isolation (PVI). The most common endpoints were freedom from AF recurrence, LVEF improvement, peak oxygen consumption, and 6-minute walking test and/or QoL questionnaires. FU was relatively short (3–12 months), and reablations were allowed and common (30%–50% of patients).

These (mostly small) RCTs dealing with the short- and mid-term effects of AF ablation showed a very positive effect of ablation, with mean LVEF increase of 11%–13% and significant improvement of exercise capacity and QoL.[7–9] However, 2 negative randomized trials compared AF ablation to best medical treatment. A study by MacDonald et al[10] that included only 41 persistent AF patients with concomitant HFrEF showed no significant improvement of LVEF as measured by MRI, probably because only 50% of the patients were in SR at the end of FU. In addition, as many as 15% of the patients suffered from ablation complications.[10]

In the AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) trial,[11] which also used LVEF improvement in MRI as a primary endpoint, there was a similar finding with a numerical but narrowly not significant increase in LVEF provided by ablation. However, early enrollment ended due to a lower than expected enrollment rate and technical issues with the MRI-provided LVEF measurements, making it challenging to draw conclusions.

In contrast, the PABA-CHF (Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure) trial, which compared "optimal rate control" by atrioventricular nodal ablation and cardiac resynchronization therapy pacing with AF

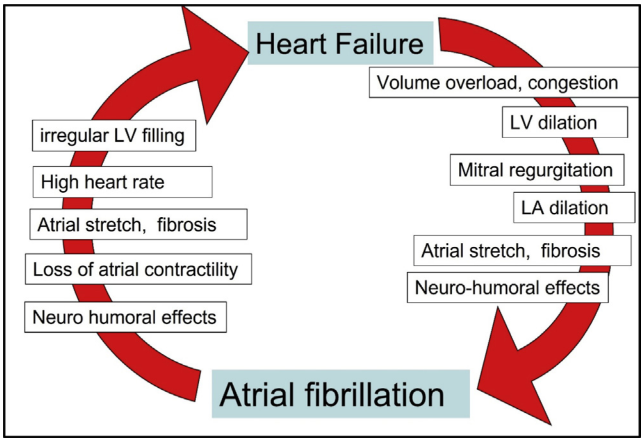

Figure 1 The vicious circle of atrial fibrillation and heart failure. LA = left atrium; LV = left ventricle.

ablation by PVI, confirmed the positive effects of ablation.[12] Even with this "drug-free, optimized" rate control, AF ablation still provided a significantly better outcome with regard to LVEF, 6-minute walking test distance, and peak O_2 consumption in patients with persistent AF and HFrEF.[12]

In conclusion, we have multiple lines of evidence that AF ablation in the context of HFrEF improves LVEF, peak oxygen consumption, 6-minute walking test, and/or QoL compared to a noninvasive medical therapy in short- to mid-term FU.

In line with this thought, Anselmino et al[4] included not only randomized but also observational data in their meta-analysis in 2014. They showed a clear benefit of AF ablation in HF patients, with a mean 13% improvement in LVEF. Importantly, they found that the benefit of AF ablation was even more pronounced if it was performed in the early stages of AF and HF.[4]

Rhythm control by ablation vs rhythm control by medication

In the AATAC (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted Device) trial, 1 RCT compared 2 rhythm control strategies—amiodarone vs catheter ablation—in patients with reduced LVEF and persistent AF. In this multicenter trial, 203 patients were randomized to either ablation (102 patients) or amiodarone treatment (101 patients) to achieve rhythm control.[13] The primary endpoint was freedom from AF/atrial tachycardia (AT) recurrence after 24 months. Secondary endpoints comprised unplanned HF hospitalizations and all-cause mortality. Forty-four percent of the patients in the ablation group were still taking amiodarone (vs 88% in the amiodarone group), whereas 22% of the amiodarone group crossed over to ablation.

The trial impressively demonstrated that in addition to the significant reduction of AF/AT recurrence achieved by

Table 1 Randomized trials comparing AF ablation in HFrEF to BMT

	No. and characteristics of patients	Endpoints	Results with regard to SR	Endpoints (major results)	Remarks
MacDonald et al	Persistent AF; 22 vs 19 rhythm vs rate control	LVEF in MRI Secondary: LVEF in MIBI; BNP	50% in SR after ablation	Primary: Failure Secondary: Yes	15% complications in ablation arm
AATAC 2016	All Pers AF, LVEF <35%; 102 vs 100 ablation vs amiodarone	Freedom from AF recurrence Secondary: Unplanned hospitalization and mortality	70% vs 40% with 1.4 ablation procedures	Primary and secondary: Positive	1.4 procedures per patient
CAMTAF (Hunter et al)	All Pers AF; LVEF <50% and NYHA ≥II; 26 vs 24 ablation vs medical rate control	LVEF at 6 months Secondary: 6mwt, peak oxygen consumption	82% in SR off AAD	Primary and secondary: Positive	1.7 procedures per patient; PVI+CFAE+lines as initial procedure
AMICA 2019	Pers AF + ls Pers AF; 68 vs 72 ablation vs best medical treatment; stopped due to futility!! Only 140 pts analyzed, although 216 should have been included	Improvement of LVEF at 12 months Secondary: 6mwt, QoL, NT-proBNP	74% in SR after 12 months vs 50%; AF burden <5% in 72% vs 44%	Primary and secondary: Negative	PVI only in 51%; 40% (in ablation) and 65% (in BMT) on amiodarone
PABA-CHF 2008	50:50 Parox AF and Pers AF; 41 vs 40 with PVI vs AVN+CRT; mean LVEF 28%	Primary composite: 6mwt, LVEF, QoL	88% and 71% (off AAD) in SR after 6 months	All compounds of primary endpoints: Positive!	PVI only; 30% in CRT group with progression of AF to persistent!
ARC-HF (Jones et al 2013)	Persistent AF LVEF <35%; randomized 26 vs 26 rhythm vs rate control	12-month peak O_2 consumption; Secondary: 6mwt, QoL, LVEF	69% after 1 ablation, 88% after up to 2 ablations	Primary and QoL: Positive; LVEF and 6mwt not. Continuous improvement over time	25% with >1 procedure; PVI+roof+mitral isthmus+CFAE
CAMERA-MRI 2017	Pers AF, LVEF <45% for unexplained CMP; 33 vs 33; mean LVEF 33%	Improvement in LVEF at 6 months (MRI) Nine secondary: LGE improvement at 6 months, QoL, AF recurrence (ILR!!), heart chamber dimensions, BNP, 6mwt	56% off drugs, 75% with AAD (33% remained on AAD, mainly amiodarone) AF burden 1.6%, only 2/33 >10%	Primary: Positive Most secondaries: Positive	PVI+posterior wall isolation (attempted in 94%, achieved in 85%)

6mwt = 6-minute walking test; AAD antiarrhythmic drug; AF = atrial fibrillation; AVN = atrioventricular node; BMT = best medical treatment; BNP = brain natriuretic peptide; CFAE = complex fractionated atrial electrogram; CMP = cardiomyopathy; CRT = cardiac resynchronization therapy; HFrEF = heart failure with reduced ejection fraction; ILR = implantable loop recorder; LGE = late gadolinium enhancement; ls = long-standing; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NYHA = New York Heart Association; Parox = paroxysmal; Pers = persistent; PVI = pulmonary vein isolation; QoL = quality of life; SR= sinus rhythm.

ablation (71% free from recurrence after ablation vs 34% with amiodarone), there was a very pronounced, significant reduction in risk of unplanned HF hospitalization (31% in the ablation group vs 56% in the amiodarone group) and all-cause death (8% in the ablation group vs 18% in the amiodarone group) provided by AF ablation.

Importantly, to achieve this high rate of SR in a cohort of persistent AF patients, a mean of 1.4 ablation procedures per patient was necessary, using an advanced ablation strategy with PVI+lines+CFAE ablation and ablation of subsequent ATs.

In conclusion, AF ablation for rhythm control was superior to amiodarone for rhythm control with regard to elimination of AF, but also for HF hospitalization and mortality. These results were mostly driven by the higher success rate of ablation in eliminating AF.

What do we know about AF ablation in HF with preserved ejection fraction?

Although the vicious circle of HF promoting AF and vice versa is present in both forms of HF, the mortality surplus caused by concomitant AF seems to be significantly more pronounced in HFrEF than in heart failure with ejection fraction (HFpEF).[14] This could explain why data on the role of AF ablation in HFpEF are more scarce and there are more observational studies than RCTs investigating the possible benefit of AF ablation (Table 2).

Table 2 Observational trials on AF ablation in HFpEF

	No. and characteristics of patients	Endpoints	Results regarding SR	Endpoints (major results)	Remarks
Machina-Ohtsuka et al 2013	74 pts with compensated HFpEF; 31% Parox AF; 59% ls Pers AF	Sinus rhythm in FU on and off AAD after single or multiple procedures; Secondary: LV strain/ TTE characteristics	Off AAD and single procedure: 27% SR after 3 years of FU; increases to 45% with multiple procedures; 73% on AAD and after multiple procedures	Multivariate predictors of SR: Other than ls Pers AF and hypertension Extensive echocardiographic assessment: all echocardiographic parameters including LV strain better in pts in SR	Extensive ablation strategy (PVI±roof line±SVC isolation±CFAE)
Castagno et al 2021	116 HCM pts; 37% Parox AF, 44% Pers AF, 19% ls Pers AF; 63% on amiodarone before ablation; 6 year of FU	Sinus rhythm in FU on and off AAD after single or multiple procedures; Secondary: Improvement in NYHA functional class	Off AAD and single procedure: 26% SR after 6 years of FU; increases to 56% with mean of 1.6 procedures	Multivariate predictors of recurrence: NYHA functional class at baseline; (ls) Pers AF; NYHA functional class significantly improved if in SR (1.6 vs 2.1)	Ablation strategy in Pers AF included PVI+2 lines±CFAE; multiple procedures; high percentage on amiodarone
STALL AF-HFpEF	35 pts diagnosed with HFpEF following invasive HFpEF confirmation (exercise right heart catheterization); 66% Pers AF	Improvement in symptoms and right heart catheterization parameters 1 year after ablation	Of 20 ablated pts, 9 (45%) in SR at 1 year	SR provided significantly better symptoms; all SR pts no longer fulfilled HFpEF criteria at invasive assessment	Incidence of occult HFpEF in AF pts probably ∼65%; invasive proof of concept that SR restoration eliminated HFpEF in these pts
Yamauchi et al 2021	502 pts. with non-Parox AF; 293/ 502 with HFpEF; 35% with ls Pers AF	AF recurrence at 1 year; symptomatic and image-based functional LV status; changes in BNP	On AAD after single ablation 83.6%; 9% with second procedure; multiple procedures on AAD success rate 92%	Comparable SR rates (all ∼95%) in no HF (125 pts), HFpEF (293 pts), and HFrEF (84 pts). NYHA status improved in all; LVEF increased and BNP decreased in both HF groups	Only ∼10% on amiodarone; not-so-extensive ablation strategy (45% with "PVI+"); PVI performed with contact force sensing/WACA

FU = follow-up; HCM = hypertrophic cardiomyopathy; HFpEF = heart failure with preserved ejection fraction; LV = left ventricle; SVC = superior vena cava; TTE = transthoracic echocardiography; WACA = wide antral circumferential ablation; other abbreviations as in Table 1.

In HFpEF, as in HFrEF, the positive effect of AF ablation on New York Heart Association (NYHA) functional classification, QoL, and 6-minute walking test seems to be linked to the ability to successfully eliminate AF in these complex patients.

However, there are conflicting data regarding the true success rate of AF ablation in HFpEF. A recent Italian observational study in HCM patients found that in a 6-year FU, multiple procedures and additional AAD treatment were needed to achieve freedom from AF/AT recurrence in 56% of patients.[15] Similarly, Machino-Ohtsuka et al[16] found in an observational study with 2-year FU that SR could be maintained in only 45% of HFpEF patients, and only by using multiple procedures and additional AAD treatment.

In contrast, in a very recent large observational study including almost 300 patients with HFpEF, Yamauchi et al[17] found that HFpEF had similar (good) ablation outcome compared to HFrEF patients and patients without HF, although a majority of patients suffered from recent onset/ paroxysmal AF.

In line with this, a recent meta-analysis showed that AF ablation in HFpEF patients results in similar success rates with regard to arrhythmia freedom and improvements in NYHA functional class and symptoms in AF-dedicated QoL scores compared to in HFrEF patients.[18]

One possible reason for the mitigated results of AF ablation in HFpEF patients is that HFpEF was often more a clinical diagnosis than an objective assessment, and dyspnea is a common symptom in AF and HFpEF equally. Thus, it can be difficult to differentiate the cause of dyspnea, and the true incidence of HFpEF in AF patients probably is underestimated. Of interest, Reddy et al[19] found that when patients with exertional dyspnea underwent exercise right heart catheterization, up to 64% suffered from occult HFpEF.

To determine the effect of AF ablation in these patients, STALL AF-HFpEF (STudy using invAsive haemodynamic measurements foLLowing catheter ablation for AF and early HFpEF) investigated patients referred for AF ablation and exertional dyspnea. Consenting patients underwent exercise right heart catheterization and were diagnosed as having HFpEF if resting pulmonary wedge pressure exceeded 15 mm Hg or during exercise exceeded 25 mm Hg.[20] Of 54 participating patients, 35 (65%) fulfilled HFpEF criteria in invasive measurements (confirming the findings by Reddy et al[19]) and underwent ablation. At 6-month invasive retesting, 9 patients (45%) no longer fulfilled the criteria for HFpEF, all of whom were in SR. After 12-month FU, 9 patients (45%) who had been successfully ablated showed significant improvement in pulmonary wedge pressure and QoL. Thus, there probably is a high rate of occult HFpEF in AF patients, and AF ablation significantly improves (symptoms of) HFpEF.

Medical treatment vs ablation: (Long-term) outcomes regarding "hard endpoints"

While the trials discussed used mostly surrogate parameters such as freedom from AF, peak oxygen consumption, LVEF, NYHA functional class, or QoL improvement as primary endpoints, mostly within short- to mid-term FU, recent large randomized trials have been designed to evaluate "hard" endpoints such as mortality, hospitalizations (for HF), and risk of stroke/transient ischemic attack in longer-term FU.

In these studies, not all of which centered on HF patients but in some instances provided subgroup analysis of HF patients, AF ablation was compared to "best medical treatment," comprising sometimes drug-promoted rate control and sometimes a mixture of AAD-driven rhythm control and rate control.

The first of these studies was CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation), in which 363 patients with LVEF <35%, implantable cardioverter-defibrillator, and AF were randomized to undergo catheter ablation (n = 179) or medical treatment (n = 184).[21] The primary endpoint was the combination of all-cause death and worsening HF hospitalization. Secondary endpoints were the single components of the primary endpoint, cardiovascular death, any hospitalization, and cerebrovascular accident. The primary and secondary endpoint results, which showed a significant benefit from AF ablation for all endpoints and a marked increase in LVEF of 8% in the ablated patients (with no change in the medical group) were published in 2018.

In the now available subgroup analyses, two very important topics were addressed more specifically. Sohns et al[22] investigated the relationship between baseline EF and the primary study endpoint and found that both patients with severely depressed EF <20% as well as those with ejection fraction between 20% and 35% benefited significantly from ablation with regard to the primary endpoint, with the latter experiencing even less often the primary endpoint. Interestingly, patients with lower NYHA functional class HF benefited even more from ablation than those with advanced NYHA functional class. Thus, ablation should be performed as early as possible, preferably before the down-spiraling of HF and AF truly begins. Brachmann et al[23] analyzed the relationship between AF burden and clinical outcomes in CASTLE-AF in the 280 of 363 patients for whom AF burden was available. They found that ablation patients who had AF burden <50% as detected by implantable cardioverter-defibrillator had a significant reduction of hard clinical outcomes such as death and (re-)hospitalizations, whereas AAD patients with a comparable AF burden reduction did not benefit from the low AF burden. This is in line with the previously presented studies. First, AF ablation has to be successful in eliminating AF in a high proportion of patients to be beneficial, and second, only rhythm control *by ablation* improves hard clinical endpoints whereas AAD-promoted rhythm control does not.

Interestingly, only AF burden reduction to <50%, but not (a single) AF recurrence >30 seconds, was associated with improved survival, thus challenging the guidelines-based, most commonly used AF ablation trial outcome measure.

The second large ablation trial dealing with hard clinical endpoints, CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation), which compared catheter ablation to AAD treatment in AF patients with and without HF, did not show a significant benefit from ablation with regard to the primary endpoint of all-cause death, stroke, cardiac arrest, and bleeding.[24]

In contrast, Packer et al[25] were able to demonstrate in the CABANA HF subgroup study, which included 778 patients with stable HF in NYHA functional class II–III, that the ablation group (378 patients vs 400 patients in the medical group) benefited significantly from ablation with regard to the primary endpoint. There was a 36% risk reduction in the composite primary endpoint and even a 43% risk reduction in all-cause mortality in the ablation group compared to the medical treatment group.

In the analysis of prespecified subgroups, the authors disclosed which subgroups benefited most and least from ablation. Elderly patients, patients with long-standing AF (12%–14% of the total cohort, respectively) and patients with ongoing risk factors for AF (sleep apnea and body mass index >30) were the groups who benefited least, and the group of long-standing AF patients was the only subgroup that did even better with medication.

Regarding stratification by LVEF, only 9% of patients included in CABANA-HF had LVEF <40%, and another 12% had EF between 40% and 50%, so the majority of patients had some form of HFpEF. Of interest, the 2 groups with EF <40% and EF between 40% and 50% did benefit numerically but not statistically significantly as a result of ablation with regard to hard clinical outcomes.

Thus, in CABANA HF, the patients who benefited most from AF ablation with regard to hard clinical outcomes, including mortality, were those with "not so long-lasting" persistent AF and patients with HFpEF. It can be speculated that the reason for this finding is that these patients have less remodeled atria with consecutively higher AF ablation success rates.

In contrast to CASTLE-AF and CABANA-HF, the recently presented RAFT-AF (Randomized ablation-based atrial fibrillation rhythm control versus rate control trial in patients with heart failure and high burden atrial fibrillation) did not show superiority of rhythm control by AF ablation over rate control (mainly by medication) in HFrEF and HFpEF patients with a composite primary endpoint of all-cause death and HF events.[26,27] Enrollment in the trial was stopped early (after 411 of 600 planned patients) because of a lower than expected enrollment rate, lower than expected event rate and perceived futility, and a numerically positive effect of AF ablation on the primary endpoint, which was not statistically significant. Because the trial is not yet published, detailed analysis for this negative result has not been performed.

AF ablation in HF—In whom and when?

In the recently published European Society of Cardiology guidelines on HF management, which mostly center on CASTLE-AF and CABANA, prudent use of AF catheter ablation is recommended (Class IIa).[28] However, the guidelines offer no differentiated view on specific patients subgroups with regard to recommendations for AF ablation.

Several metaanalyses comparing AF ablation vs medical therapy in HF patients have been published (Table 3). In line with the previously presented data, AF ablation resulted in significantly reduced mortality and HF hospitalization and improved LVEF, 6-minute walking test, and/or QoL.[29–31] In these meta-analyses, there are hints that AF ablation might not be beneficial in all subsets of HF patients.

Because the positive effect of AF ablation in HF is based, to a great extent, on the ability to reduce significantly AF burden, patient subgroups with lower AF ablation success are likely to benefit less from AF ablation in HF. This includes elderly patients (age >75 years); patients with (long-standing) persistent AF, large LA diameter, or prevalent LA fibrosis; and those with cumulative risk factors for

Table 3 Meta-analysis/stratified pooled data on AF ablation and HF

	Included trials	Endpoints	Result of AF ablation	Outcome regarding endpoints	Remarks
Anselmino et al 2014	36 trials (RCT, observational) with HFrEF and AF ablation included (1838 pts)	Long-term safety and outcome of AF ablation in HFrEF; predictors of recurrence; impact on LV function	SR in 54%–67% (mean 60%); 4.2% complications	LVEF improved by mean 13%; multivariate analysis: Time since AF diagnosis and advanced HF with worse, no SHD with better prognosis	AF ablation should be performed early in AF and HF history; positive effect of AF ablation is preserved over long-term FU
Asad et al 2019	18 RCTs; AF ablation vs MT with subgroup analysis of HFrEF pts	Primary outcome: all-cause mortality Secondary: Hospitalization and arrhythmia recurrence	Significant reduction of arrhythmia recurrence with AF ablation; ablation equally successful in pts with and without HFrEF	Significant reduction of mortality, hospitalization with ablation, driven by HFrEF pts	Positive effects of AF ablation especially in HF pts; younger pts benefited more from ablation
Chen et al 2020	Stratified pooled analysis of 11 RCT; subset A: AAD rhythm control vs. rate control; subset B: AF ablation rhythm control vs. MT	Primary outcome: All-cause mortality Secondary: rehospitalization, stroke, LVEF, arrhythmia recurrence, QoL	SR in 70.4% ablated pts vs 19.9% MT	Only rhythm control by ablation reduces significantly all-cause mortality, rehospitalization; mean of 11% increase in LVEF after AF ablation	Subset A (medical rhythm control) did NOT benefit from rhythm control strategy, whereas subset B (rhythm control by ablation) All studies with "PVI+" strategies and mostly multiple ablation procedures
Pan et al 2021	6 RCTs included, comparing AF ablation to MT in HFrEF pts	Primary outcome: Mortality Secondary: (Re-) hospitalization, LVEF, QoL	Significant reduction of arrhythmia recurrence in ablation group compared to MT group	Significant reduction of mortality and all secondary endpoints significantly better with ablation than MT	No subgroup analysis Ablation is better, probably because of better SR maintenance

HF = heart failure; RCT = randomized controlled trials; SHD = structural heart disease; other abbreviations as in Tables 1 and 2.

AF (eg, hypertension, sleep apnea, obesity, chronic kidney disease).

In a nationwide Korean health database analysis, Yang et al[32] found that, although AF ablation resulted in a significant reduction in all-cause mortality, cardiovascular death, HF hospitalizations, and stroke/transient ischemic attack, the subgroup of elderly patients (age >75 years) did not benefit from AF ablation with regard to cardiovascular death. Regarding the type of AF, Okada et al[33] found that the amount of LV reverse remodeling on computed tomography is dependent on the type of AF recurrence after ablation, with a gradual decrease in the incidence of LV reverse remodeling ranging from no AF recurrence (83% with reverse remodeling) to paroxysmal AF (81%) and persistent AF (63%). Because the type of AF recurrence was associated with the baseline type of AF, persistent AF patients had a less favorable outcome than patients with paroxysmal AF.

As discussed in the section "outcomes regarding hard endpoints", there are hints from the CASTLE-AF as well as CABANA HF trials that patients with (too) advanced HF do not benefit from AF ablation, even if SR maintenance is achieved. In line with this, Ukita et al[34] analyzed in an observational study predictors for LVEF improvement after AF ablation. Forty-nine of 81 patients with HFrEF showed improved LVEF after 6 months. Although in univariate analysis the absence of ischemic CMP, LV end-diastolic dimension <53 mm before ablation, and freedom from AF recurrence were significantly associated with LVEF improvement, only preablation LV end-diastolic dimension <53 mm remained a predictive factor for LVEF improvement after catheter ablation. This reduced effect of AF ablation in patients with more dilated LVs and those with advanced HF might be explained by the already too advanced, irreversible ventricular fibrosis in these terminally ill patients. However, even in these "worse" subgroups, the outcomes of ablation are still (numerically) better than those with medication, and because the complication rates of ablation now are low, AF ablation is a valuable treatment option, even more so with a pragmatic combination of ablation and, for example, amiodarone.

Conclusion

Catheter ablation of AF in the setting of HF is associated with a clear benefit over medical therapy, not only with regard to symptoms and QoL but also hard clinical endpoints such as mortality, hospitalizations, and LVEF. This benefit is driven mainly, but not exclusively, by the improved rhythm control resulting from ablation. Importantly, rhythm control using AF ablation is associated with improved clinical outcome even compared to AAD-obtained rhythm control, probably due to the deleterious side effect profile of AAD. Thus, AF ablation in HF should be performed early and accompanied by comprehensive AF risk factor reduction.

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