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CATHETER ABLATION OF ATRIAL FIBRILLATION IN PATIENTS WITH SYSTOLIC LEFT VENTRICULAR DYSFUNCTION

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Atrial fibrillation (AF) is the most common arrhythmia among the adult population, affecting up to 2% of the population. Among patients with chronic heart failure (CHF), the prevalence of AF reaches 12.3%. The presence of common risk factors and pathophysiological mechanisms of AF and CHF development lead to the frequent combination of these two pathologies, which has a negative impact on the course of the underlying disease and further prognosis, increasing the chances of adverse outcomes such as stroke, myocardial infarction, and cardiovascular mortality. The results of most randomized studies indicate that interventional treatment of AF in patients with CHF and intermediate to low left ventricular ejection fraction (LV) contributes to reducing the functional class of CHF and improving quality of life, but at the same time, there is currently no consensus on the effectiveness, safety, and extent of catheter intervention. In this review, we attempted to summarize the literature data regarding the outcomes of interventional treatment of AF in patients with systolic LV dysfunction.

Key words: atrial fibrillation; chronic heart failure; low left ventricular ejection fraction; catheter ablation; pulmonary vein isolation

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Atrial fibrillation (AF) is the most common arrhythmia among the adult population [1]. According to the EP-OCHA study [2], AF is diagnosed in an average of 2.04% of the population. The prevalence of this arrhythmia increases significantly in older age groups and among individuals with concomitant cardiovascular pathology, reaching 12.3% in patients with chronic heart failure (CHF). Moreover, increasing life expectancy, improved diagnostic methods, and broader access to medical care are expected to result in a 2.3-fold increase in newly diagnosed cases of AF in the coming decades [1].

The prevalence of CHF, according to Russian studies in 2020, was 7% in the general population [3]. The EP-OCHA-HF study indicated a growth in CHF prevalence from 6.1% to 8.2% over the past 20 years [4]. AF is a causative factor in the development of CHF in 12.3% of cases [4]. Furthermore, there is a well-established epidemiological link between AF and myocardial infarction (MI) [5], contributing to the development of CHF in patients with AF who have experienced MI. Shared risk factors and pathophysiological mechanisms underlying AF and CHF frequently result in their coexistence, which negatively affects disease progression and prognosis [6, 7].

Data from the RIF-HF multicenter registry, which studied the clinical course of CHF combined with AF and the prognostic significance of the arrhythmia [8], revealed that cardiovascular mortality and the risk of adverse outcomes over a one-year observation period varied significantly depending on the left ventricular ejection fraction (LVEF). Cardiovascular mortality in patients with CHF and AF was 4.1% in those with preserved LVEF (HFpEF), compared to 9.3% and 15.5% in patients with moderately reduced LVEF (HFmrEF) and reduced LVEF (HFrEF), respectively ($p < 0.001$). The incidence of a composite endpoint (stroke, MI, cardiovascular death) was 22% and 25.5% in the HFmrEF and HFrEF groups, respectively ($p < 0.001$) [8]. These findings underscore that AF in patients with left ventricular systolic dysfunction remains a pressing issue in modern healthcare.

According to current guidelines for the diagnosis and management of AF [1], catheter ablation with pulmonary vein isolation (PVI) is the first-line therapy for patients with AF and left ventricular dysfunction (Class I recommendation, Level of Evidence B). The results of most randomized studies, including PABA-CHF [9], Jones D. [10], CAMTAF [11], AATAC [12], CAMERA-MRI

[13], CASTLE-AF [14], CABANA [15], AMICA [16], and RAFT-AF [17], demonstrate that interventional treatment of AF in patients with left ventricular dysfunction contributes to reducing the functional class (FC) of CHF and improving quality of life. However, there is currently no consensus on the effectiveness, safety, and scope of catheter interventions.

The objective of the study is to summarise current literature on the outcomes of interventional treatment of AF in patients with left ventricular systolic dysfunction.

The search and selection of publications on studies concerning the interventional treatment of AF in patients with chronic heart failure (CHF) were conducted using two databases: the Cochrane Library of Systematic Reviews (<http://www.thecochranelibrary.com>) and the Medline bibliographic database (<http://www.ncbi.nlm.nih.gov/pubmed>). Additional searches were performed using Google Scholar with the following keywords: atrial fibrillation, chronic heart failure, low ejection fraction, catheter ablation, pulmonary vein isolation. A total of 88 articles were analysed, resulting in a final list of 37 publications relevant to the review. Three key areas of focus were identified: the pathophysiological aspects of AF and CHF, the efficacy of radiofrequency ablation (RFA) of AF in patients with CHF, and the impact of interventional treatment of AF on the long-term prognosis of patients with AF and CHF.

PATHOPHYSIOLOGICAL ASPECTS OF AF AND CHF

Atrial fibrillation and CHF are two distinct nosological entities that can occur independently. However, they frequently develop concomitantly, as each condition can induce and perpetuate the other, forming so-called “vicious cycles” in pathogenesis. The interplay between AF and CHF is rooted in shared pathophysiological mechanisms. AF disrupts both systolic and diastolic cardiac functions, potentially leading to an increased incidence of CHF. Con-

versely, the structural and neurohormonal changes characteristic of CHF, whether with preserved or reduced LVEF, elevate the likelihood of AF onset and worsen disease prognosis. AF and CHF share common risk factors—advanced age, arterial hypertension, diabetes mellitus, obesity, smoking, and sleep apnea syndrome—all of which independently raise the risk of developing both conditions (Figure 1)[18].

THE EFFECTIVENESS OF CATHETER ABLATION

Interventional treatment of AF has undergone significant advancements over a relatively short period, transitioning from atrioventricular node ablation (AVN) [19, 20] to standardized protocols for pulmonary vein isolation (PVI) [21] and high-density electroanatomical mapping [22]. Interest in interventional treatment of AF in patients with CHF began in 2004, with the publication of Michael S. Chen’s study evaluating the efficacy and safety of catheter ablation of AF in patients with systolic LV dysfunction [23].

Between 2008 and 2022, 10 randomized clinical trials (RCTs) investigated the features of interventional treatment of AF in patients with CHF. These studies varied significantly in terms of average follow-up duration, ranging from 6 months in the PABA-CHF trial [9] to 4 years in the CAMERA-MRI [24] and CABANA [25] studies. Most trials focused on patients with persistent AF, such as the studies by M.R. McDonald (2010) [26], D.G. Jones (2013) [10], CAMTAF [11], AATAC [12], CAMERA-MRI [13], and AMICA [16]. Patients with paroxysmal AF were included in PABA-CHF [9], CASTLE-AF [14], CABANA [15, 25], and RAFT-AF [17], with their proportion in the study groups ranging from 9% [17] to 49% [9].

The percentage of patients with ischemic etiology of CHF also varied considerably, with the lowest proportion (23%) in the CAMTAF study [11], 30–40% in RCTs by D.G. Jones (2013) [10] and RAFT-AF [17], over 40% in AMICA [16], and more than 60% in PABA-CHF [9] and AATAC [12]. The size of study groups also differed widely, from fewer than 50 participants in PABA-CHF [9], M.R. McDonald (2010) [26], D.G. Jones (2013) [10], CAMTAF [11], and CAMERA-MRI [13], to 50–100 participants in AMICA [16] and CABANA [25], and more than 100 in AATAC [12], CASTLE-AF [14], and RAFT-AF [17]. The average LV ejection fraction (LVEF) in the study groups ranged from 18% (M.R. McDonald (2010) [26]) to 45% (CABANA [25]). Cardiac MRI was used to assess LVEF in the studies by M.R. McDonald (2010) [26], D.G. Jones (2013) [10], and CAMERA-MRI [13].

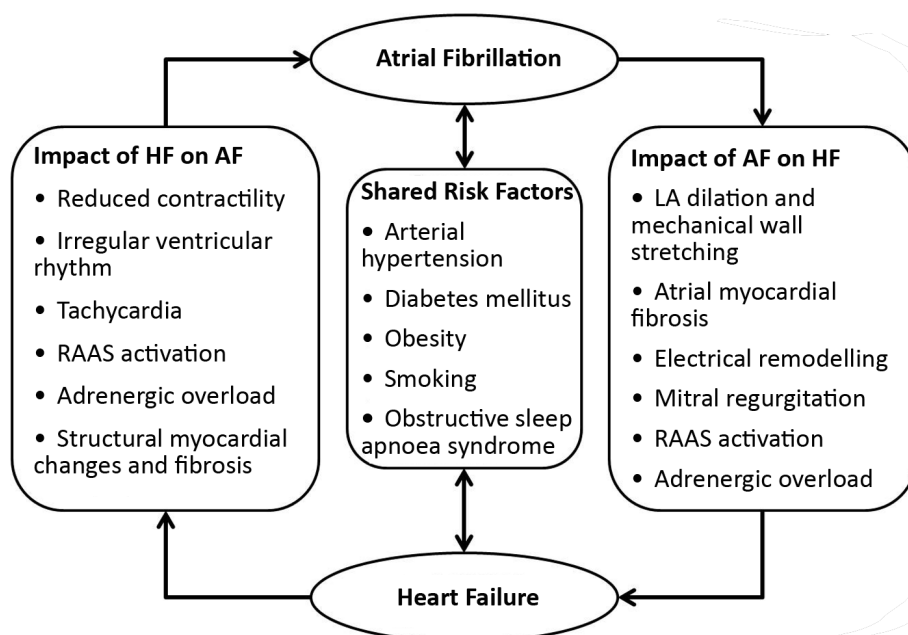


Figure 1. Pathophysiological relationship between atrial fibrillation and heart failure. Abbreviations: HF - heart failure; AF - atrial fibrillation; RAAS - renin-angiotensin-aldosterone system; LA - left atrium.

In addition to PVI, ablation strategies in these RCTs included non-pulmonary vein targets such as roofline ablation in the left atrium (LA), mitral isthmus, and posterior wall isolation. In PABA-CHF [9], CASTLE-AF [14], CABANA [25], AMICA [16], and RAFT-AF [17], the extent of non-pulmonary vein ablation was left to the operator's discretion. CAMERA-MRI [13] included posterior wall isolation along with PVI, while CAMTAF [11] used a strategy combining PVI with ablation of complex fractionated atrial electrograms (CFAEs), roofline, and mitral isthmus ablation. In AATAC [12], CFAE ablation was paired with roofline and superior vena cava isolation. D.G. Jones (2013) [10] implemented an extensive ablation strategy involving PVI, roofline, mitral isthmus, CFAE, and cavotricuspid isthmus ablation.

The operator's experience requirements also varied: a minimum of 50 procedures was required in CASTLE-AF [14] and 100 in CABANA [25]. Intervention standards included intracardiac echocardiography (PABA-CHF [9], AATAC [12]), general anesthesia (D.G. Jones (2013) [10], CAMERA-MRI [13]), and high-density mapping with a multipolar catheter (D.G. Jones (2013) [10]). AF recurrence was assessed using previously implanted intracardiac devices (CASTLE-AF [14]) or loop recorders implanted during catheter ablation (CAMERA-MRI [13]).

The duration of antiarrhythmic drug (AAD) therapy after catheter ablation varied, ranging from 4–6 weeks [13, 17] to 3–6 months [9, 12, 14]. In some cases, it continued beyond these periods if necessary. In the studies by D.G. Jones (2013) [10] and CAMTAF [11], AADs were discontinued immediately after ablation. Control groups across all RCTs included patients with AF and CHF who received medical therapy, with strategies focused on rate control (PABA-CHF [9], M.R. McDonald (2010) [26], D.G. Jones (2013) [10], CAMTAF [11], CAMERA-MRI [13], RAFT-AF [17]), rhythm control (AATAC [12]), or optimal medical therapy (CASTLE-AF [14], CABANA [15, 25], AMICA [16]).

Comparison of Catheter Ablation for AF with Rate Control Strategies

The first RCT on this topic, 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), was published in 2008 [9]. This study included 81 patients with AF and New York Heart Association (NYHA) Class II–III CHF (LVEF <40%). Participants were randomized into an intervention group (n=41) and a group receiving biventricular pacemaker implantation with subsequent AV node ablation (n=41). Six months post-intervention, 88% of patients in the catheter ablation group were free from AF (71% without antiarrhythmic drugs), with no progression to persistent AF (0% vs 30%, $p<0.001$), a greater 6-minute walk test distance (340 m vs 297 m, $p<0.001$), and improved LVEF (35% vs 28%, $p<0.001$). However, this was associated with a higher rate of perioperative complications (17%) compared to AV node ablation.

It is worth noting that earlier studies, such as RACE [27], AFFIRM [28], and AF-CHF [29], did not identify significant differences in mortality, quality

of life, or stroke rates between rhythm control and rate control strategies with medication. However, the authors of PABA-CHF concluded that non-pharmacological treatment of AF is highly effective and superior to rate control via AV node ablation.

In 2010, a study by M.R. McDonald compared systolic LV function in patients with persistent AF and advanced CHF following interventional treatment (n=22) or pharmacological rate control (n=19) [26]. After 14 months, the success rate of interventional AF treatment was 50%. Unlike PABA-CHF, this study did not find significant differences in LVEF improvement (4.5% in the radiofrequency ablation (RFA) group vs 2.8% in the rate control group, $p=0.6$), nor in the 6-minute walk test or quality of life. The perioperative complication rate for RFA was 15% [26].

A similar study design was employed in the 2013 RCT by D.G. Jones, which included patients with persistent AF and CHF (LVEF <35%) randomized to catheter ablation (n=26) or pharmacological rate control (n=26) [10]. After 12 months, sinus rhythm was maintained in 88% of the catheter ablation group (including repeat procedures, 69% without antiarrhythmic drugs). The authors noted a trend toward improved 6-minute walk test distance ($p=0.095$) and myocardial contractility (LVEF +5.6%, $p=0.055$) following catheter ablation compared to rate control.

Further evaluation of rhythm control via RFA (n=26) and pharmacological rate control (n=24) in patients with persistent AF and systolic LV dysfunction (LVEF <50%) was conducted in the CAMTAF trial, published in 2014 [11]. After 6 months, the success rate of repeated interventions was 81%, with 38% success after a single procedure. At 12 months, 73% of patients remained AF-free without antiarrhythmic drugs. Unlike the studies by M.R. McDonald (2010) and D.G. Jones (2013), the CAMTAF trial reported significant LVEF improvement in the RFA group (from $32\pm 8\%$ to $40\pm 12\%$), with no improvement in the rate control group ($34\pm 12\%$ to $31\pm 13\%$, $p=0.015$). Patients with sustained sinus rhythm experienced improved quality of life, though the perioperative complication rate for RFA reached 7.7%.

In 2017, results from the CAMERA-MRI trial (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction) were published [13]. This study included patients with persistent AF and CHF (mean LVEF $33\pm 8.6\%$), randomized to catheter ablation or pharmacological rate control. One month post-ablation, 75% of patients were AF-free (56% without antiarrhythmic drugs). At 6 months, both groups showed significant LVEF improvement (18.3% in the RFA group, $p<0.001$; 4.4% in the rate control group, $p=0.0145$). Substantial LVEF recovery ($\geq 50\%$) was observed in 58% of the catheter ablation group compared to 9% in the rate control group ($p<0.001$). Catheter ablation was also associated with reverse LV remodeling (reduction in LV end-diastolic and end-systolic volumes) and left atrial volume. The authors concluded that catheter ablation significantly reduced NT-proBNP levels, improved exercise tolerance, NYHA class, and quality of life. The perioperative complication rate was 6%.

In 2020, long-term results of CAMERA-MRI were published [24]. Four years post-ablation, sinus rhythm was maintained in 43% of patients. LVEF improvement was significantly greater in the RFA group ($16.4 \pm 13.3\%$) compared to the rate control group ($8.6 \pm 7.6\%$, $p=0.001$).

In the RAFT-AF study, published in 2022, rhythm control with RFA ($n=124$) was compared to rate control ($n=116$) in patients with paroxysmal or persistent AF and CHF [17]. The minimum follow-up period was 2 years. The study found no significant difference in the primary endpoint (mortality and CHF decompensation) between groups (23.4% vs 32.5% , $p=0.066$). However, the RFA group demonstrated significantly improved LVEF ($10.1 \pm 1.2\%$ vs $3.8 \pm 1.2\%$, $p=0.017$), increased 6-minute walk test distance (44.9 ± 9.1 m vs 27.5 ± 9.7 m, $p=0.025$), better quality of life according to the Minnesota Living with Heart Failure Questionnaire (least squares mean difference: -5.4 , 95% CI 1.7 - 10.7 , $p=0.0005$), and greater reductions in NT-proBNP levels (mean change: -77.1% vs -39.2% , $p<0.0001$) [17].

Comparison of Catheter Ablation for AF with Rhythm Control Strategies

The AATAC (Ablation vs Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRT-D) randomized clinical trial (RCT), published in 2016, compared catheter ablation of AF ($n=102$) with amiodarone therapy ($n=101$) in patients with persistent AF and CHF (LVEF $<40\%$) [12]. Unlike previous RCTs, which focused on comparing non-pharmacological rhythm control strategies with rate control (via medication or AV node ablation), this study assessed rhythm control efficacy through catheter ablation versus pharmacological intervention (amiodarone loading dose of 10 g over two weeks, followed by a maintenance dose of 200 mg). The mean follow-up period was 24 months. The study demonstrated higher efficacy of interventional treatment compared to amiodarone therapy (70% vs 37% , $p<0.001$), as well as significant reductions in all-cause mortality (8% vs 18% , $p=0.037$) and unplanned hospitalizations (31% vs 57% , $p<0.001$). The perioperative complication rate for catheter ablation was 8.1% .

Comparison of Catheter Ablation with Optimal Medical Therapy

Long-term outcomes of AF treatment were further evaluated in the multicenter CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial, published in 2018 [14]. This study enrolled patients with paroxysmal or persistent AF and NYHA class II-IV CHF (LVEF $\leq 35\%$), randomized to interventional treatment ($n=179$) or medical therapy ($n=184$, $\sim 30\%$ rhythm control, $\sim 70\%$ rate control). The average follow-up period was 37 months. The primary composite endpoint (death or hospitalization due to CHF decompensation) occurred significantly less often in the catheter ablation group compared to the medical therapy group (28.5% vs 44.6% , $p=0.006$). LVEF values increased by 8% after catheter ablation versus 0.2% with medical therapy after 60 months ($p=0.005$), and freedom from AF recurrence was achieved in 63.1% and 21.7% of patients, respectively ($p<0.001$). The perioperative complication rate was 7.8% .

The results of the multicenter CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial were published in 2019 [15]. This study compared catheter ablation ($n=1108$) with medical therapy ($n=1096$) in terms of efficacy and its impact on adverse outcomes (death, stroke, bleeding, or ventricular fibrillation/asystole). The median follow-up period was 48.5 months. No significant differences were observed between the groups for the primary composite endpoint (8.0% vs 9.2% , $p=0.3$). However, subgroup analysis of patients with CHF showed a 36% reduction in the primary endpoint (hazard ratio [HR] 0.64 , 95% confidence interval [CI] 0.41 - 0.99) and a 43% reduction in all-cause mortality (HR 0.57 , 95% CI 0.33 - 0.96) in the catheter ablation group compared to patients receiving medical therapy [25].

A 2019 study, AMICA, further evaluated catheter ablation of AF ($n=68$) versus optimal medical therapy ($n=72$) in patients with persistent AF and CHF (mean LVEF 28%) [16]. The authors did not find any significant advantages of catheter ablation over medical therapy after one year, primarily due to comparable increases in LVEF between the two groups (8.8% vs 7.3% , $p=0.36$).

IMPACT OF CATHETER ABLATION ON PROGNOSIS IN PATIENTS WITH AF AND CHF

Interest in interventional treatment for AF began in 2004 and primarily focused on evaluating efficacy, safety, and its impact on CHF progression (e.g., changes in left ventricular ejection fraction [LVEF], exercise tolerance, quality of life, and CHF functional class). Long-term outcomes were first reported in 2015 when T.J. Bunch et al. published a 5-year follow-up study of 267 patients with AF and CHF (LVEF $\leq 35\%$) after a single catheter ablation procedure for AF [30]. Comparison groups included patients with AF and CHF receiving medical therapy ($n=1068$) and patients with CHF without AF ($n=1068$). At the end of the 5-year follow-up, all-cause mortality rates were 27% , 55% , and 50% , respectively ($p<0.001$). The reduction in mortality in the catheter ablation group was attributed to lower cardiovascular mortality. Unlike most earlier studies, the authors did not observe significant differences in LVEF changes between the groups but identified a substantial reduction in CHF-related hospitalizations in the catheter ablation group. Additionally, T.J. Bunch et al. noted a trend toward fewer strokes in the catheter ablation group, although this difference was not statistically significant.

The AATAC randomized controlled trial (RCT) published in 2016 [12] also demonstrated lower mortality and fewer unplanned hospitalizations in the catheter ablation group compared to the amiodarone therapy group (8% vs. 18% , $p=0.037$; 31% vs. 57% , $p<0.001$, respectively) during the 2-year follow-up period.

The outcomes of adverse cardiovascular events and mortality in patients with AF and CHF after catheter ablation were published by J. Geng et al. in 2017 [31]. The catheter ablation group included 90 patients and was compared to a heart rate control group of 304 patients. The follow-up period was 13.5 ± 5.3 months. Adverse cardiovascu-

lar events occurred significantly less often in the catheter ablation group (13.3% vs. 29.3%, $p=0.005$). The catheter ablation group also demonstrated lower rates of mortality, stroke, and unplanned hospitalizations compared to the rate control group (3.3% vs. 7.9%, 4.4% vs. 9.9%, and 10.0% vs. 16.1%, respectively), though these differences did not achieve statistical significance.

The study of mortality and CHF decompensation following catheter ablation compared to medical therapy was extended in the CASTLE-AF RCT [14]. Over a 37-month follow-up period, mortality rates were 13.4% and 25.0% ($p=0.01$), and hospitalization rates for CHF decompensation were 20.7% and 35.0% ($p=0.004$), respectively.

The results of observations in patients with AF and CHF (LVEF $\leq 45\%$) were published by S. Ichijo in 2018 [32]. Freedom from adverse events (death, stroke, or hospitalization due to CHF decompensation) at 1, 2, 3, and 4 years after the last intervention was 97.6%, 97.6%, 97.6%, and 88.7%, respectively. These findings highlight the significance of catheter ablation in managing patients with systolic left ventricular dysfunction and AF.

A review of current publications on interventional treatment of AF in CHF patients reveals that most authors report significant improvements in LVEF, CHF functional class (NYHA), quality of life, and exercise tolerance in patients with paroxysmal and persistent AF and CHF following CA [9-14, 16-17, 23-24, 32]. Several studies also demonstrated improved long-term outcomes, including reduced mortality and cardiovascular events, in this patient cohort [12, 14, 25, 30-32]. However, RCT found no advantages of CA over medical therapy in improving LVEF and CHF functional class [16, 26] or reducing long-term mortality [17].

The identification of predictors for LVEF improvement following interventional treatment of AF remains a pressing issue. A. Rillig et al. (2015) [33] and W. Ullah et al. (2016) [34] demonstrated the importance of sinus rhythm maintenance in improving LVEF. J. Kosiuk et al. (2014) [35] and M. Wang et al. (2017) [36] noted the greatest LVEF improvements in patients with the most severe systolic dysfunction. The CAMERA-MRI study [13, 24] identified the absence of myocardial fibrosis on gadolinium-enhanced cardiac magnetic resonance imaging as an independent predictor of LVEF improvement. R. Hunter et al. (2014) [11] reported that the absence of ischemic heart disease predicted

better LVEF outcomes. Conversely, A. Pott et al. (2020) [37] found that pulmonary hypertension was a strong and independent predictor of LVEF non-improvement in patients with this condition (odds ratio [OR] 0.15, 95% confidence interval [CI] 0.041–0.540, $p=0.004$). However, these findings were not confirmed in other studies.

LVEF improvement is associated with various mechanisms of cardiac chamber remodeling. Sinus rhythm maintenance [33, 34] facilitates effective atrial systole, thereby increasing the overall left ventricular stroke volume. Tachycardia suppression optimizes atrial systolic contribution to ventricular filling, yielding the best outcomes at a heart rate of 50–80 beats per minute [18]. Additionally, the presence of viable myocardium [11, 13, 14] may be critically important for left ventricular remodeling and improved systolic function.

It is worth noting that no universally accepted model currently exists to predict LVEF changes after interventional treatment of AF in patients with systolic left ventricular dysfunction. The rate of intraoperative complications in this patient group remains a significant concern. The average complication rate in RCTs was 10.7%, ranging from 6% [13] to 17% [9].

CONCLUSION

The appropriateness of interventional treatment for AF in patients with systolic left ventricular dysfunction is supported not only by existing publications but also by the current clinical guidelines for AF diagnosis and treatment. However, the data on the efficacy and safety of catheter ablation for AF, as well as on the optimal extent of lesion creation, vary significantly. This underscores the need for further research in this area.

In our view, it is particularly important to focus on identifying clinical predictors of perioperative complications and AF recurrence, determining risk factors for cardiovascular events in the long-term follow-up period, and developing a clinical model for selecting patients with systolic left ventricular dysfunction who are most likely to benefit from interventional treatment for AF while maintaining an acceptable risk of procedural complications. Establishing such a model would facilitate decision-making regarding the necessity of interventional procedures (including repeat interventions), taking into account the anticipated efficacy and long-term prognosis.

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