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Atrial fibrillation ablation in heart failure patients: new therapeutic hope

Ablacja migotania przedsionków u pacjentów z niewydolnością serca — nowe nadzieje terapeutyczne

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Abstract

Atrial fibrillation (AF) and heart failure (HF) are common cardiovascular diseases and their coexistence is associated with a worse prognosis in terms of severity of HF symptoms, AF treatment effectiveness, HF hospitalization, and HF-related mortality. In search of optimal therapeutic solutions for this patient group, the authors of this study review current research on the use AF ablation in patients with HF. Analysis of published literature provides scientific evidence supporting the superiority of catheter ablation over conventional pharmacological management, primarily in terms of reducing mortality in this patients group.

Key words: atrial fibrillation, catheter ablation, heart failure

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Introduction and epidemiology

Atrial fibrillation (AF) is the most common sustained supraventricular tachyarrhythmia. In 2010, it was estimated that AF affected 8.8 million people in the European Union, and by 2060, this number is projected to increase to 17.9 million [1]. The lifetime risk of developing AF in the European population of European descent at the age of 55 is 37.1% [1]. The prevalence of AF in adults is 2–4%, and it continues to rise [1]. One hypothesis explaining the increasing incidence of AF is the aging of the population and the probable vascular background associated with hypertension, atherosclerosis, increased arterial stiffness, leading to impaired left ventricular (LV) diastolic function and volume overload of the left atrium [2].

Atrial fibrillation and heart failure (HF) often coexist [2]. AF can be the cause or the consequence of HF. Approximately 40% of patients with AF or HF eventually develop the other condition [3]. In the Dutch PREVEND cohort study, it was revealed that the incidence rate of HF with reduced left ventricular ejection fraction (LVEF < 40%) per 1000 person-years was 12.75 in the AF population compared to 1.99 in the cohort without AF (relative hazard: 5.79). In the case of HF with preserved LV systolic function, the corresponding rates were 4.9 in the AF group versus 0.85 in the non-AF group (relative hazard: 4.8) [4]. The

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coexistence of HF and AF is associated with worse prognosis, and the development of *de novo* AF in the course of HF is an adverse prognostic factor [2]. In the ACALM registry, which included 929,552 inpatients in Northern England from 2000 to 2013, patients with HF and concomitant AF had the highest mortality rate (70.8%). Among patients with HF and sinus rhythm, the mortality rate was 64.1% (70.8 vs. 64.1%; $p < 0.001$), in the AF population without HF, it was 45.1%, whereas the population without HF and AF had the lowest mortality rate (11.7%) [5]. AF leads to left atrial enlargement, reduced blood flow to the left ventricle, dilation of the mitral and tricuspid valve rings, resulting in their insufficiency, progressive fibrosis within the heart, shortened diastolic period, hemodynamic, metabolic, and neurohormonal changes leading to the development/progression of HF [6, 7]. The development of HF secondary to AF (tachyarrhythmia-induced cardiomyopathy) is associated with relatively good prognosis [8].

Rhythm control vs. rate control — which is better?

Atrial fibrillation therapy, in addition to crucial anticoagulant treatment, involves adopting either a strategy to maintain sinus rhythm (rhythm control strategy) or focusing on controlling the ventricular rate without aiming to maintain sinus rhythm (rate control strategy).

The results of the EAST-AFNET 4 randomised, multicentre international clinical trial, published in 2020, demonstrated the superiority of an early rhythm control strategy over a rate control therapy. The study included 135 centres and enrolled 2789 patients with newly diagnosed AF (within one year of inclusion in the study). In the group of 1395 patients, a rhythm control strategy aiming to maintain sinus rhythm was implemented, while the remaining 1394 patients were treated with a rate control strategy. The majority of patients in the rhythm control group initially received antiarrhythmic drugs (including 35.9% flecainide, 19.6% amiodarone, 16.7% dronedarone), and 8% of this population underwent ablation (the percentage of patients undergoing ablation in this group increased to 19.4% after 2 years). The early rhythm control strategy was associated with a reduction in the primary composite endpoint including death from cardiovascular causes, stroke, hospitalisation due to HF exacerbation, and hospitalisation due to acute coronary syndrome compared to the rate control strategy group (3.9 vs. 5.0 events/100 person-years; $p = 0.005$) [9]. These results indicate the benefits of an early rhythm control strategy, in which catheter ablation is undoubtedly an important tool. It should be emphasised that this study demonstrated the advantages of introducing rhythm control within one year of AF diagnosis, and patients with AF diagnosed more than 12 months prior were not included in the study, so no conclusions can be drawn regarding the choice of strategy for patients with longer-standing AF.

The role of ablation in atrial fibrillation according to current guidelines

According to the currently applicable guidelines of the European Society of Cardiology regarding the diagnosis and treatment of AF from 2022, catheter ablation for pulmonary vein isolation (PVI) is recommended as a rhythm control strategy for AF patients who have failed therapy with a single class I or III antiarrhythmic drug or are intolerant to these drugs, to alleviate symptoms in patients with paroxysmal AF (class I, level of evidence A), persistent AF without major risk factors for AF recurrence (class I, level of evidence A), or persistent AF with major risk factors for AF recurrence (class I, level of evidence B). Regardless of symptoms, when there is a high likelihood of tachyarrhythmia-induced cardiomyopathy, PVI ablation is advisable to reverse LV ventricular systolic dysfunction (class I, level of evidence B). Catheter ablation should be considered in patients with AF and HF with reduced ejection fraction (HFrEF) to reduce mortality and hospitalisations (class IIa, level of evidence B). Failure to achieve rate control through intensive pharmacotherapy or intolerance to it is an indication for considering atrioventricular node ablation and pacemaker implantation (class IIa, level of evidence B). In HFrEF patients, the presence of indications for cardiac resynchronisation therapy should always be considered. The guidelines strongly emphasise patient preferences in the choice of treatment method [3].

Atrial fibrillation ablation

Ablation is an attractive alternative to antiarrhythmic drugs for heart rhythm control in AF patients and is associated with a lower risk of arrhythmia recurrence [10–13]. The benefits of using ablation as a first-line treatment, instead of antiarrhythmic therapy, have been demonstrated in terms of a reduced risk of recurrence, with a similar safety profile [14, 15].

In AF, the main ablation technique is PVI using either radiofrequency or cryoablation. Both methods show similar efficacy and safety [16, 17]. Another emerging technique is pulse field ablation, although further research is needed to assess its effectiveness [18].

Since the publication of the latest European Society of Cardiology guidelines on AF management and HF guidelines, new scientific evidence has emerged regarding the use of PVI ablation in patients with both AF and HF. A meta-analysis published in 2022 by Romero et al. [19], which included 8 randomised clinical trials (a total of 2121 patients with a mean age of 65 ± 5 years, 72% being male), demonstrated significantly lower mortality (8.8% vs.

13.5%; p = 0.0005), reduced risk of arrhythmia recurrence (3.9% vs. 69.6%; p = 0.0003), and greater increase in LVEF (+9.4 ± 7.6% vs. +3.3 ± 8%; p < 0.00001) in patients undergoing catheter ablation for AF compared to pharmacotherapy in this patient population [19].

The available knowledge on the use of AF ablation in HF can be summarised for different subpopulations of patients (Table 1).

Atrial fibrillation ablation in HFrEF

According to studies conducted to date, catheter ablation of AF in HFrEF patients is an effective method to maintain sinus rhythm and is associated with an increase in LVEF, improvement in both quality of life and physical performance. However, there may be a need for re-ablation to achieve long-term maintenance of sinus rhythm [20]. This is an

Tabela 1. Zestawienie badań dotyczących zastosowania ablacji w grupie chorych z migotaniem przedsionków i niewydolnością serca (omówienie w tekście)

Study (publication year)	Size of the study group and type of intervention	Characteristics of the study population	Observation period	Results
Jones et al. [21] (2013)	52 patients (26 undergoing PVI, 26 conservative strategy)	• persistent AF • symptomatic HF with LVEF ≤ 35%	12 months	There was a higher peak oxygen uptake in the ablation group (+2.13 vs. –0.94 mL/kg/min; p = 0.018)
CAMTAF [22] (2014)	50 patients (26 undergoing ablation — mean LVEF was 32 ± 8%; 24 rhythm control — mean LVEF 34 ± 12%)	• persistent AF • symptomatic HF and LVEF < 50%	6 months	The ablation-treated group showed: • greater increase in LVEF (40 ± 12 vs. 31 ± 13%; p = 0.015) • higher peak oxygen uptake (22 ± 6 vs. 18 ± 6 mL/kg/min; p = 0.014) • better quality of life as determined by the Minnesota questionnaire (24 ± 22 vs. 47 ± 22; p = 0.001)
AATAC [23] (2016)	203 patients (102 undergoing ablation, 101 treated with amiodarone)	• HF in NYHA functional class II–III • LVEF < 40% • persistent AF	2 years	Among patients treated with ablation there was: • lower mortality (8 vs. 18%; p = 0.037) • lower need for unplanned hospitalisations (31 vs. 57%; p < 0.001) • maintenance of sinus rhythm (70 vs. 34%; p < 0.001)
AMICA [24] (2019)	140 patients (68 underwent ablation, 72 rhythm control and rate control)	• persistent/sustained AF • congestive HF with LVEF ≤ 35%	1 year	Study terminated prematurely due to no demonstrated benefit in the ablation treatment group
CASTLE-AF [25] (2018)	363 patients (179 ablated, 184 treated conservatively)	• paroxysmal/persistent AF • HF in NYHA functional class II–IV • LVEF ≤ 35%	60 months	In the group that received PVI ablation, there was: • a reduction in the primary composite endpoint (mortality + unplanned hospitalisations for CHF, 28.5 vs. 44.6%; p = 0.006) • lower incidence of hospitalisation for HF (20.7 vs. 35.9%; p = 0.004) and cardiovascular disease (35.8 vs. 48.4%; p = 0.04) • lower mortality from cardiovascular disease (11.2 vs. 22.3%; p = 0.009) • lower mortality from any cause (13.4 vs. 25.0%; p = 0.01)

Study (publication year)	Size of the study group and type of intervention	Characteristics of the study population	Observation period	Results
RAFT-AF [26] (2022)	• a total of 411 patients • 197 patients (116 with LVEF ≤ 45% and 81 with LVEF > 45%) underwent a ventricular rate control strategy • 214 qualified for AF ablation (124 with LVEF ≤ 45%, 90 with LVEF > 45%)	More than 4 AF attacks in the last 6 months or persistent AF < 3 years	Minimum 2 years	The study showed no differences between the study groups
DECAAF II [29] (2023)	843 patients (421 patients underwent extended ablation, 422 patients underwent classic PVI ablation)	Persistent AF	1 year	The application of the ablation procedure resulted in an increase in LVEF in each subpopulation by: • HFrEF: 16.66 ± 11.9%; p < 0.001 • HFmrEF: 10.74 ± 8.34%; p < 0.001 • HFpEF: 8.39 ± 11.43%; p < 0.001
Rattka et al. [32] (2021)	86 patients (43 patients treated with transcatheter PVI balloon cryoablation and 43 patients with drug therapy)	AF and HFpEF	Mean 32 ± 22 months	Use of the ablation procedure resulted in: • improved left ventricular diastolic function • lower incidence of recurrent arrhythmias • fewer hospitalisations for HF, cardiovascular disease and hospitalisations for any cause • lower severity of HF symptoms
CABANA — subanalysis on HF patients [33] (2021)	Out of 2204 patients included in the study, 778 patients with HF were identified (of whom 378 were treated with ablation and 400 with conservative treatment)	• AF • aged 65 years or older, or younger than 65 years, but with 1 or more risk factors for stroke • HF (NYHA class ≥ II, no division according to LVEF)	48 months	In the ablation-treated group, the following was demonstrated: • 36% reduction in the composite endpoint of death, disabling stroke, major bleeding or cardiac arrest for the ablation-treated group • 43% reduction in mortality • 44% reduction in AF attacks • improvement in quality of life for the ablation-treated group
CAMERA-MRI [40] (2020)	66 patients (33 ablation-treated, 33 drug-treated)	Patients with left ventricular systolic dysfunction, without other than AF as a gripping cause	4 years	Greater increase in LVEF in ablation-treated patients (16.4 vs. 8.6%; p = 0.001), more frequent normalisation of LVEF (46.8 vs. 20%; p < 0.05), lower proportion of patients with LVEF < 35% (46.8% to 8.5%; p < 0.001) compared to control group

AF — atrial fibrillation; HF — heart failure; HFmrEF — heart failure with mildly reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; LVEF — left ventricular ejection fraction; PVI — pulmonary vein isolation

effective method for reducing mortality in this age group and slowing down the progression of HF [19].

The first randomised clinical trial regarding AF ablation in HFrEF patients was conducted by Jones et al. [21] in 2013. The study included 52 patients with symptomatic HF, LVEF ≤ 35%, and persistent AF. Twenty-six patients underwent ablation, while 26 received rate control therapy. In the 12-month follow-up period, the ablation group showed a greater peak oxygen uptake (+2.13 vs. –0.94 mL/kg/min; p = 0.018) compared to the control group [21].

The CAMTAF trial, a randomised clinical trial, compared the effectiveness of PVI ablation with rate control therapy

in patients with persistent AF, symptomatic HF, and LVEF < 50%. The study included 26 patients who underwent ablation (mean LVEF 32 ± 8%) and 24 patients who received rhythm control therapy (mean LVEF 34 ± 12%). In the 6-month follow-up period, the ablation group showed higher LVEF values (40 ± 12% vs. 31 ± 13%; p = 0.015), higher peak oxygen uptake (22 ± 6 vs. 18 ± 6 mL/kg/min; p = 0.014), and improved quality of life assessed using the Minnesota Living with Heart Failure Questionnaire (24 ± 22 vs. 47 ± 22; p = 0.001) compared to the rhythm control group [22].

The AATAC trial was a multicentre, randomised clinical trial that included patients with HF in New York Heart Association (NYHA) functional class II–III, LVEF < 40%, and persistent AF. One hundred and two patients underwent catheter ablation, and 101 patients received treatment with amiodarone. In the two-year follow-up period, the ablation group demonstrated lower mortality (8% vs. 18%; p = 0.037) and a lower rate of unplanned hospitalisations (31% vs. 57%; p < 0.001) compared to patients treated with amiodarone. At the end of the follow-up period, a higher proportion of patients in the ablation group maintained sinus rhythm (70% vs. 34%; p < 0.001) [23].

In the randomised AMICA clinical trial, which included patients with persistent or long-standing persistent AF, congestive HF with an initial LVEF ≤ 35%, the effectiveness of ablation treatment was compared with treatment without ablation (rhythm control — including electrical cardioversion, rate control). The study included 140 patients, of whom 68 underwent ablation. The follow-up period lasted for one year. The study did not show any benefits of ablation in this patient group, which led to its premature termination [24].

The CASTLE-AF trial was a randomised clinical trial that included patients with paroxysmal or persistent AF, lack of efficacy or intolerance to pharmacotherapy, HF in NYHA class II-IV, LVEF ≤ 35%, in order to accurately record AF recurrence. Patients with implanted cardioverter-defibrillator, resynchronisation therapy systems, or electrocardiogram telemetry devices were enrolled in the study. The study included 179 patients who underwent ablation and 184 patients treated conservatively. The PVI group had significantly lower mortality and unplanned hospitalisations due to worsening HF — the primary composite endpoint (28.5% vs. 44.6%; p = 0.006), a lower rate of HF-related hospitalisations (20.7% vs. 35.9%; p = 0.004), cardiovascular diseases (35.8% vs. 48.4%; p = 0.04), and any cause (63.7% vs. 66.3%; p = 0.96), cerebrovascular incidents (2.8% vs. 6.0%; p = 0.15), lower cardiovascular mortality (11.2% vs. 22.3%; p = 0.009), and lower all-cause mortality (13.4% vs. 25.0%; p = 0.01). The results of the CASTLE-AF trial contributed to the increase in the indication class for PVI ablation in the HF and AF patient group [25].

The published results of the randomised RAFT-AF clinical trial, which involved 21 centres in 4 countries, provided new data on the use of ablation in patients with HF and AF. The trial included 411 patients with more than 4 episodes of AF in the last 6 months or persistent AF lasting less than 3 years. One hundred and ninety-seven patients (116 with LVEF ≤ 45% and 81 with LVEF > 45%) underwent rate control strategy, and 214 were selected for AF ablation (124 with LVEF ≤ 45% and 90 with LVEF > 45%). In the group of patients with LVEF ≤ 45% at baseline, lower mortality or HF-related incidents were noted compared to the rate control group (22.6% vs. 37.1%; p = 0.059), greater reduction in natriuretic peptide levels (–77.1% vs. –39.2%; p < 0.001), and greater increase in LVEF (10.1 ± 1.2% vs. 3.8 ± 1.2%; p = 0.017). In the group of patients with LVEF > 45% at baseline, the use of ablation was mainly associated with a greater decrease in natriuretic peptide levels, with a minor impact on mortality and other measured parameters. The results of the study did not reach statistical significance due to relatively small differences and low number of patients (percent not reaching statistical significance: –0.9%). The use of ablation was associated with a significant reduction in AF occurrence in this patient group compared to the control group [26].

Atrial fibrillation ablation in HFmrEF patients

Data on this patient group are limited due to frequently adopted LVEF values that do not clearly distinguish the HF with mildly reduced ejection fraction (HFmrEF) population from the studied group.

Valuable data regarding ablation in this patient group are provided by the results of the DECAAF II trial. It was a prospective, multicentre study comparing the effectiveness of standard PVI ablation with ablation of extended PVI areas imaged with magnetic resonance imaging (MRI) [27]. The study included 843 patients with persistent AF. Extended ablation was performed in 421 patients and standard PVI ablation in 422. There were no significant differences in the effectiveness of both techniques, although ablation extended to areas of fibrosis imaged with MRI was associated with a higher incidence of adverse events [28]. The analysis of the study results was performed for individual subpopulations of patients with HFrEF, HFmrEF, and HF with preserved ejection fraction (HFpEF). The study showed an increase in LVEF in all HF subpopulations (in HFrEF: 16.66 ± 11.9; p < 0.001, in HFmrEF: 10.74 ± 8.34; p < 0.001, in HFpEF: 8.39 ± 11.43; p < 0.001). The study did not demonstrate a difference in the frequency of AF recurrences in patients with and without HF. The researchers noted that the improvement in LVEF was not dependent on the degree of atrial fibrosis [29].

Atrial fibrillation ablation in HFpEF patients

Diagnosing HF in patients with AF and preserved LVEF is challenging because many symptoms such as dyspnoea or increased fatigue are common to both HF and AF [30]. Both diseases involve diastolic dysfunction of the left ventricle and increased natriuretic peptide levels [30]. Moreover, the possibilities of effective pharmacological treatment for HFpEF are significantly lower compared to HFrEF, which raises hopes for potential therapeutic options, including AF treatment in this patient group.

It is worth mentioning that the coexistence of HFpEF is associated with a higher risk of AF recurrence after percutaneous ablation than the general population [31].

In a German single-centre study that included 127 AF and HFpEF patients hospitalised between 2013 and 2018, after the numbers of patients in both groups were balanced, an analysis was performed on 43 patients treated with catheter baloon cryoablation for PVI and 43 patients treated pharmacologically. In the ablation group, improvement in LV diastolic function, lower frequency of arrhythmia recurrences, fewer hospitalisations due to HF, cardiovascular diseases, and hospitalisations for any cause were observed. Furthermore, patients treated with ablation had less severe HF symptoms (according to the NYHA scale) and lower levels of natriuretic peptides [32].

Also of note is the randomised CABANA clinical trial, which included 2204 patients with AF, aged 65 years and older, or younger than 65 but with 1 or more stroke risk factors. One of the sub-analyses of this study evaluated patients with HF and AF who underwent ablation or pharmacological treatment, however, it was performed for the entire HF group without dividing them into HFrEF, HFmrEF, HFpEF. The analysis was based on the real treatment of AF and HF patients, not according to how they were randomised to the study (intention-to-treat analysis). The study included 778 patients with HF, of whom 378 underwent ablation and 400 received pharmacological treatment. Initial LVEF value was known for 571 patients, with a median LVEF in the studied population of 55%, and patients with LVEF ≤ 35% accounted for only 7.9%. The study showed a 36% reduction in the composite endpoint comprising death, disabling stroke, major bleeding, or cardiac arrest in the ablation-treated group. Moreover, the study also showed a 43% reduction in mortality during the 48-month follow-up period, a 44% reduction in AF episodes, and an improvement in quality of life in this ablation-treated group [33].

The meta-analysis conducted by Androulakis et al. [34] was the first to focus on the role of rhythm control strategy using ablation in HFpEF patients. In the analysis, primary ablation was performed in 80.3% of cases, with the majority of patients maintaining sinus rhythm in the long term. During the long-term follow-up period (ranging from 10.3 to 38 months, depending on the trial), AF recurred in 22.3% of patients. The ablation procedure was relatively safe, with a low incidence of complications, and resulted in reduced mortality and reduced hospitalisation rates. The authors highlighted the need for further randomised clinical trials in this patient group [34].

Another meta-analysis involving 1696 patients analysed the use of AF ablation in HFpEF patients and patients without HF. The rate of maintenance of sinus rhythm was similar in both groups. The use of ablation reduced the incidence of hospitalisations secondary to HF compared with pharmacologically treated patients; however, there was no reduction in mortality in the group of patients who underwent PVI ablation [35].

Atrial fibrillation ablation in patients with suspected or diagnosed tachycardia-induced cardiomyopathy in the course of atrial fibrillation

Persistent AF is one of the best-known causes of tachyarrhythmic cardiomyopathy [36]. PVI ablation proved to be significantly superior to atrioventricular node ablation with secondary pacemaker implantation [37].

In the meta-analysis by Dagres et al. [38], which included 9 clinical trials (total of 354 patients with reduced LVEF in the course of AF), PVI ablation revealed a positive effect on LVEF increase (mean increase of 11.1%; $p < 0.001$) [38].

The CAMERA-MRI trial was a multicentre, open label, prospective, randomised clinical trial investigating the impact of catheter ablation on LVEF during a 4-year follow-up period. The study included 66 patients with no other detectable cause of LVSD other than AF, half of whom received ablation and the other half received rate-control treatment. The applied treatment resulted in an LVEF increase of 16.4% in patients who underwent ablation and 8.6% in patients who underwent pharmacological rate control (16.4 vs. 8.6%; $p = 0.001$). During the 4-year follow-up period, normalisation of LVEF occurred in 46.8% of patients who underwent ablation and 20% of patients treated pharmacologically (46.8 vs. 20%; $p < 0.05$). Ablation led to a reduction in the percentage of patients with LVEF < 35% from 46.8% to 8.5%; $p < 0.001$ (while in the rate control group, the percentage of patients with LVEF < 35% decreased from 53.3% to 33.3% ($p = 0.08$) [39]. Moreover, it was proved that effective PVI ablation in tachycardia-induced cardiomyopathy associated with AF reversed adverse ventricular remodeling and reduced ventricular fibrosis [40].

Conclusions

The emerging data from an increasing number of randomised multicentre clinical trials seem to unequivocally point to the benefits of using catheter ablation in patients with AF and HF. This makes it possible to consider ablation not only as an equivalent treatment to the pharmacological rhythm control strategy but as a treatment associated with a better prognosis. The use of invasive treatment is

associated with reduced mortality and HF progression in the discussed patient population. The growing scientific evidence can and should result in a wider use of of this therapeutic option, considering patient preferences, and it is expected that ablation will occupy a stronger position in future guidelines for this patient group.

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Streszczenie

Migotanie przedsionków (AF) i niewydolność serca (HF) są częstymi schorzeniami układu krążenia, a ich współwystępowanie wiąże się z gorszym rokowaniem w aspekcie nasilenia objawów niewydolności krążenia, skuteczności leczenia AF, hospitalizacji z powodu HF oraz śmiertelności z powodu HF. W poszukiwaniu optymalnych rozwiązań terapeutycznych dla tej grupy chorych, autorzy niniejszej pracy, dokonali przeglądu aktualnych badań dotyczących zastosowania zabiegu ablacji AF u pacjentów z HF. Analiza opublikowanego piśmiennictwa dostarcza dowodów naukowych na przewagę postępowania z wykorzystaniem ablacji przezcewnikowej nad klasycznym postępowaniem farmakologicznym, przede wszystkim pod postacią redukcji śmiertelności w tej grupie chorych.

Słowa kluczowe: migotanie przedsionków, ablacja, niewydolność serca

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