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Hybrid Therapy in the Management of Atrial Fibrillation

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Abstract: Atrial fibrillation is the most common sustained arrhythmia. Because of the sub-optimal outcomes and associated risks of medical therapy as well as the recent advances in non-pharmacologic strategies, a multitude of combined (hybrid) algorithms have been introduced that improve efficacy of standalone therapies while maintaining a high safety profile. Antiarrhythmic administration enhances success rate of electrical cardioversion. Catheter ablation of antiarrhythmic drug-induced typical atrial flutter may prevent recurrent atrial fibrillation. Through simple ablation in the right atrium, suppression of atrial fibrillation may be achieved in patients with previously ineffective antiarrhythmic therapy. Efficacy of complex catheter ablation in the left atrium is improved with antiarrhythmic drugs. Catheter ablation followed by permanent pacemaker implantation is an effective and safe treatment option for selected patients. Additional strategies include pacing therapies such as atrial pacing with permanent pacemakers, preventive pacing algorithms, and/or implantable dual-chamber defibrillators are available. Modern hybrid strategies combining both epicardial and endocardial approaches in order to create a complex set of radiofrequency lesions in the left atrium have demonstrated a high rate of success and warrant further research. Hybrid therapy for atrial fibrillation reviews history of development of non-pharmacological treatment strategies and outlines avenues of ongoing research in this field.

Keywords: Atrial fibrillation, catheter ablation of arrhythmias, pharmacological antiarrhythmic therapy, hybrid therapy.

INTRODUCTION

Currently, atrial fibrillation (AF) is the most common sustained arrhythmia. Overall prevalence has reached 5.5% with an incidence rate of 9.9/1,000 person-years, both increasing dramatically with age. In the Rotterdam study, the prevalence of AF for people aged 55 to 59 years was 0.7% with an incidence of 1.1/1,000 person-years, whilst above 85 years of age, the prevalence increased to 17.8%. The highest incidence was identified in the age group 80 to 84 years reaching 20.7 per 1,000 [1]. The figures are generally higher in men than in women with an overall prevalence of 6%, respective 5.1% and incidence rates of 11.5, respective 8.9/1,000 person-years [1].

Atrial fibrillation represents a serious heart rhythm disorder associated with substantial mortality and morbidity. In the Framingham Heart study, patients with AF were at 1.5- to 1.9-fold higher risk of death compared to those with sinus rhythm [2]; paradoxically, women demonstrating greater mortality risk than men. The most encountered cause of death was ischemic heart disease, stroke and/or other cardiovascular conditions [2]. The presence of AF is also associated with a higher incidence of stroke [3], heart failure [4] or cognitive dysfunction [5].

Over the last two decades, the prevalence of atrial fibrillation has significantly increased, predominantly in developed countries of Western Europe and North America [6]. From 1980 to 2000, the incidence of AF increased by 12.1% and it is projected to reach nearly 16 million affected individuals in the USA by 2050 [7]. Expanding to epidemic proportions, atrial fibrillation accounts for a substantial increase in cardiac-related hospitalizations, and is linked to the worst outcomes of all-cause hospitalizations and consequently is resulting in an increase in overall health care costs [8].

Management strategies for the treatment of AF are very limited. The results of conventional pharmacologic therapy are far from optimal and are restricted with many complications. Long-term efficacy of antiarrhythmic drug therapy depends critically on the AF form and other comorbidities and hardly surpasses 50%, even with high-efficiency drugs such as amiodarone [9], [10]. A significant drawback is the occurrence of numerous adverse effects, not to mention the proarrhythmic potential of antiarrhythmic drugs which can yield fatal consequences. The CAST study was the first to confirm the risk in the 1980s [11]. The antiarrhythmic agents only have a suppressive effect which means the need for lifelong drug therapy which represents significant restriction of the treatment, mainly for young patients who are for decades subjected to the administration of potentially harmful and expensive medication.

Poor efficacy and the disputable nature of antiarrhythmic therapy has prompted a search for non-pharmacologic control of AF as early as in the late 1980s. Due to paucity of satisfactory treatment options, so-called hybrid therapy combining both a pharmacologic and non-pharmacologic approach in varying permutations was introduced.

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The concept of hybrid therapy is based on a synergy of different therapeutical strategies, mainly pharmacotherapy coupled with other techniques. The history of the method introduced some bizarre combinations as well as many successful approaches which have been employed in the management of AF until now. Herein we review the 30-year long history of hybrid therapy for atrial fibrillation with a focus on methods still used as well as outlining the future prospects.

ELECTRICAL CARDIOVERSION AND ANTIARRHYTHMIC DRUG THERAPY

Using electrical cardioversion to terminate cardiac arrhythmia and restore the sinus heart rhythm is a routine clinical practice. The success rate of electrical cardioversion can be influenced by many factors, namely by the duration of the arrhythmia, size of the atrium, patient's age, comorbidities or pretreatment with antiarrhythmic drugs. The beneficial effect of prescribing antiarrhythmics prior to electrical cardioversion has been proven by several clinical studies, particularly for agents of class IA and III, class IC with dispute.

The most effective antiarrhythmic drug facilitating electrical cardioversion in patients with atrial fibrillation is considered to be Ibutilide [12]. Pretreatment with ibutilide was associated with significantly lower energy requirements for defibrillation. Such a compelling effect was also documented with amiodarone [13] and sotalol [14]. The effect of propafenone has not been proven, however, propafenone administration significantly reduced the early recurrence of atrial fibrillation [15].

Electrical cardioversion is still frequently used in the management of atrial fibrillation and pretreatment with antiarrhythmic drugs has become a routine method of enhancing the procedure's efficacy. Agents of class IC and III are among the most prescribed.

CATHETER ABLATION OF CAVOTRICUSPID ISTHMUS (CTI) AND ANTIARRHYTHMIC DRUG THERAPY

Catheter ablation has been developed to become one of the most common non-pharmacological management strategies for cardiac arrhythmias. Since the late 20th century, catheter ablation is a treatment of choice for a wide range of arrhythmias, monomorphic supraventricular arrhythmias in particular [16].

With respect to the complex pathophysiology of atrial fibrillation, the present-day procedure is based on creating intricate patterns of circular and linear lesions, mostly in the left atrium. The complex anatomy of the left atrium and technical difficulties related to reaching the left atrium and performing this effective and safe procedure had impeded progress in ablation techniques for atrial fibrillation as compared to interventions for monomorphic supraventricular arrhythmias. Thus, it was not until the first decade of the 21st century that effective non-pharmacological strategies based on the complex ablation procedure in the left atrium have been developed and only recently that they have gained widespread acceptance. The method is now suggested as first-line treatment for selected subgroups of patients [17].

Conversely, catheter ablation of typical atrial flutter has been a simple, well-established and high-efficiency management strategy for more than two decades. The mechanism of typical atrial flutter was defined as macroreentrant tachycardia originating from the right atrium with an area of slow conduction within the cavotricuspid isthmus [18]. The aim of the procedure is to interrupt the right atrial macroreentry circuit by linear application of radio-frequency energy in the cavotricuspid isthmus between the tricuspid valve annulus and the inferior vena cava. Inhibiting conduction in this pathway curatively treats typical atrial flutter with an acute success rate of nearly 100% and achieving a bidirectional block of CTI (a conduction block in both directions) provides long-term success in over 90% of cases [19-23].

A relationship between atrial fibrillation and typical atrial flutter has been recognised and known for a long time. Mutual anatomical substrate accounts for mutual occurrence of these arrhythmias. Both anatomy of the right atrium with multiple barriers and conduction properties in the presence of atrial fibrillation contributes to facile spontaneous conversion of AF to a stable atrial flutter [24]. Likewise, the conversion is well documented after initiation of antiarrhythmic drug therapy [25].

Ablation of cavotricuspid isthmus as a stand-alone therapy in patients with atrial fibrillation has been proven to be unsuccessful. The only exception are selected patients with atrial fibrillation convertable to typical atrial flutter by the administration of antiarrhythmic agents. In those patients, catheter ablation of cavotricuspid isthmus and continuation of initiated antiarrhythmic therapy have shown to be a highly effective strategy [26] (See Fig. **1**). The agent used in the trial was flecainide, but similar results were obtained for amiodarone [27], propafenone [28] and sotalol [29]. In these studies, the recurrence of atrial fibrillation was significantly reduced to 20-42%. The only variable associated with recurrent AF was a history of associated pre-ablation episodes of atrial fibrillation while on antiarrhythmic treatment [29], (see Fig. **2**).

Catheter ablation of CTI for antiarrhythmic drug-induced typical atrial flutter has therefore remained in the standard armamentarium of interventional electrophysiologists. The method is not inferior to complex ablation and produces a considerably lower risk for patient. Compared to complex interventions, the procedure is simple, faster, and less prone to adverse events. This notion is important for the elderly, polymorbid or less co-operative patients, in whom a complex procedure with its time consuming and demanding nature may not be feasible. Thus, a hybrid therapy could be a reasonable option for those patients.

LINEAR RADIO-FREQUENCY ABLATION LESIONS IN THE RIGHT ATRIUM AND ANTIARRHYTHMIC DRUG THERAPY

As previously mentioned, non-pharmacological ablation therapy of atrial fibrillation has been evolving since the late 1980s. The primary objective was to create a set of non-conductive linear and circular lesions by means of surgical

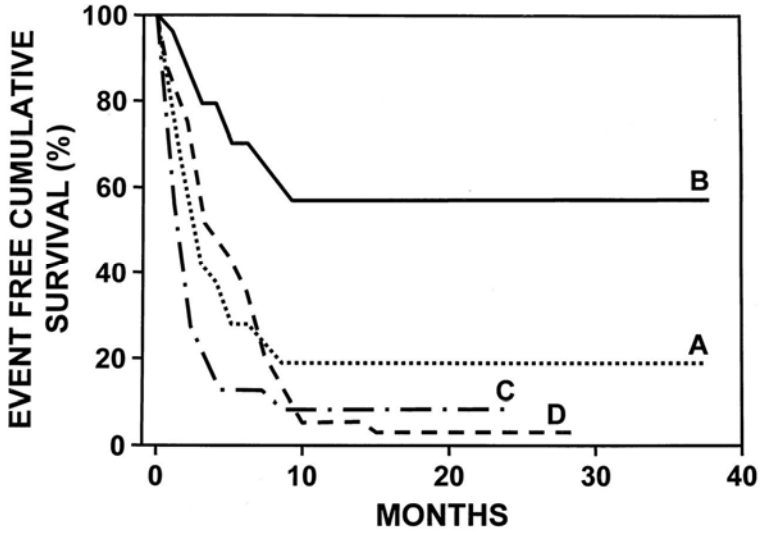


Fig. (1). Atrial fibrillation- and atrial flutter-free cumulative survival curves for the four patient groups (A–D). (A) Farmacologic treatment, n=23, (B) Farmacologic treatment + conventional radiofrequency ablation (RFA) of CTI, n=24, (C) conventional RFA CTI, n=24, (D) Control group – patients with non-inducible typical atrial flutter submitted to RFA CTI, n=37. Courtesy of Stabile *et al*., 2001 [26].

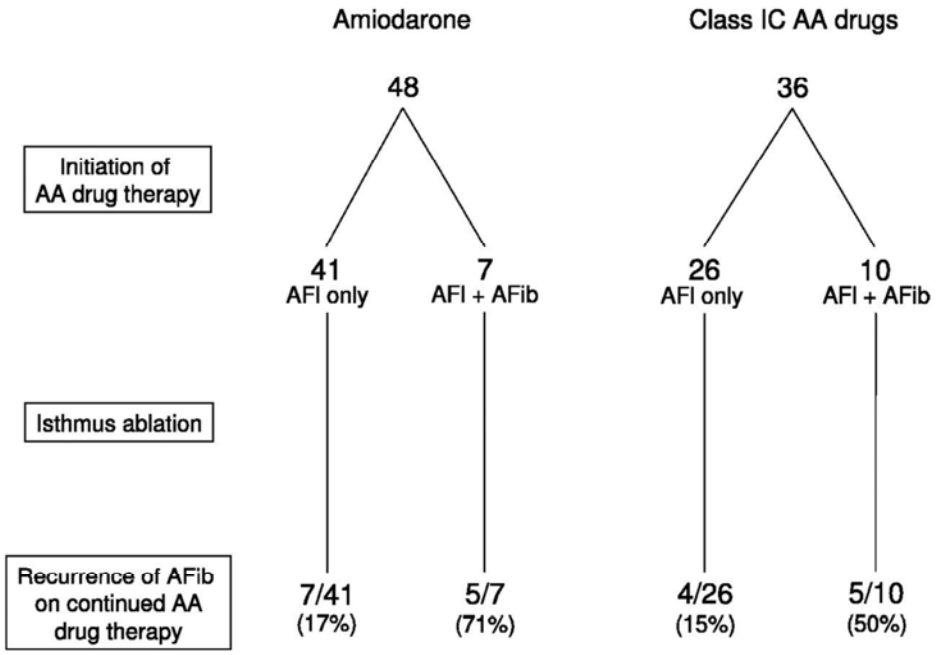


Fig. (2). Recurrence of atrial fibrillation (AFib) on continued antiarrhythmic (AA) drug therapy in patients with atrial flutter only (AFl only) and patients with accompanying pre-ablation episodes of atrial fibrillation (AFl+AFib). Comparison of amiodarone and class IC antiarrhythmic (AA) drugs (flecainide, propafenone). Courtesy of Reithmann *et al*., 2003 [29].

incisions and to electrically compartmentalise the atria. After achieving a critical size of the sections, arrhythmia was eliminated and the procedure restored the normal sinus rhythm [30-32]. Promising results of these surgical interventions had prompted the development of safer and less aggressive techniques of atrial catheter ablation. The durability of the concept was proved in animal models [33] and the first cases reporting successful performance in humans soon followed [34].

In 1996, the first study in a larger population of patients with paroxysmal atrial fibrillation has been published [35]. Linear ablation lesions in the left atrium were shown to be superior to lesions performed in the right atrium in preventing AF episodes with an efficacy rate of 60% vs 33%. Despite limited success, studies with right atrial linear lesions have been performed due to safer and simpler ablation in this heart chamber [36]. Right atrial ablation has proven successful only when combined with a regimen of previously ineffective antiarrhythmic drugs while procedural complications were comparable to complex ablations in the left atrium.

According to a meta-analysis published in 2012 [37], which included data from six different trials involving 189 patients, this hybrid approach was successful in 82% of cases. However, this therapy has only a palliative effect re-

sulting in relief from symptoms of AF, not preventing arrhythmic episodes altogether, and it also necessitates continuation of an initial antiarrhythmic drug regimen, whereas non-pharmacologic therapy aims primarily at its discontinuation. To our knowledge, this strategy has been rendered obsolete with the advance of catheter ablation techniques, operators' expertise and less complications related to complex left atrial procedures.

COMPLEX CATHETER ABLATION IN THE LEFT ATRIUM COMBINED WITH ANTIARRHYTHMIC DRUG THERAPY

Over the last few decades, a complex catheter ablation in the left atrium (or both atria) has proven to be the most effective management strategy for atrial fibrillation. The objective is to create a complex set of circular and linear lesions of ablation. These interventions now employ irrigated-tip catheters and are guided by 3D electro-anatomical mapping systems. The approach results have had a high success rate of 66% to 89%, being further improved by repeated ablation in patients with recurrent arrhythmia and thus reaching 76% to 93% [38]. Procedural success can vary widely depending on many factors. First of all is the type of AF; significantly better results are observed in paroxysmal forms of atrial fibrillation. Comorbidities, underlying organic heart disease or frequency of post-ablation rhythm monitoring are among the other predictors of a poorer clinical outcome. In spite of being currently the most effective therapeutic option, left atrial catheter ablation has not shown desirable results in a number of patients. The addition of pharmacologic therapy to the routine strategy of catheter ablation enhances the overall success of the procedure.

The effectiveness of this approach was verified by several studies and register data. However, short-term administration of antiarrhythmic medication does not provide long-term improvement in procedure success. Leong-Sit *et al.* in a randomised trial examined 110 patients undergoing catheter ablation in the left atrium for the management of paroxysmal atrial fibrillation. The findings demonstrated that antiarrhythmic drugs administered during the first six weeks after the procedure decreases early recurrence of arrhythmias, but proved there was no difference in the prevention of arrhythmia recurrence at six months follow-up between patients on and off medication [39]. Transient use of corticosteroids shortly after catheter ablation for atrial fibrillation has shown to be more promising. Koyama *et al.* investigated the outcome of a three-day administration of corticosteroids (intravenous hydrocortisone and oral prednisolone) in a randomised, placebo-controlled trial of 125 patients in whom pulmonary vein isolation for paroxysmal atrial fibrillation was performed. Treatment with corticosteroids decreased immediate recurrence of AF and atrial flutter (7% to 31%). Although not being adequately powered, the reduction in atrial arrhythmia recurrence at 14 months was also documented (85% to 71%, $P < 0.032$) [40].

The most preferred hybrid treatment of the present day is a combination of complex catheter ablation and long-term antiarrhythmic drug therapy. As stated above, the efficacy of ablation for atrial fibrillation is not as high as for ablation of simple arrhythmias, but can be improved by long-term use of antiarrhythmic medication. Multiple, small, non-randomised trials and register data investigated this management strategy. In 2009, Calkins *et al.* conducted an extensive meta-analysis and literature review of 63 studies on the efficacy of catheter ablation for atrial fibrillation. The single-procedure success rate of radio-frequency ablation without antiarrhythmic drugs therapy was 57%; with multiple procedures efficacy rose to 71%. Overall procedural success of antiarrhythmic drug therapy was 77% [41]. The largest worldwide report on these management strategies has been published by Cappato *et al.* in 2010. In a questionnaire survey, they collected data from 182 centres in which complex catheter ablation for atrial fibrillation was performed on 16,309 patients. After a mean follow-up period of 18 months, the intervention was considered successful in 70% of patients without antiarrhythmic therapy and in 80% of patients on previously ineffective antiarrhythmic regimen. The highest efficacy rates were reported in patients with paroxysmal atrial fibrillation as 74.9% (off medication) and 83.2% (on antiarrhythmic therapy) in comparison to persistent AF (64.8% and 75%) and long-lasting AF (63.1% and 72.3%) [42]. A positive correlation between the age of a patient and a high percentage of antiarrhythmic medication after catheter ablation of AF was documented by Zado *et al.* [43]. In 2008, he published a study of 1,165 patients who underwent a complex catheter ablation for atrial fibrillation. Patients were randomly assigned to three age groups (<65 years, 65-74 years and ≥ 75 years). No relevant difference was found between the groups in overall success rates (89%, 84%, 86%, P=NS). The proportion of patients remaining on previously ineffective antiarrhythmic drugs to successfully control AF was 20%, 29%, 37% (P=0.024), respectively. However, some of those patients have continued their antiarrhythmic drug regimen even in the absence of recurrences of AF (5%, 13%, 14%, P = 0.004). A strong trend towards relatively poorer success of ablative procedure and more frequently ongoing antiarrhythmic medication in patients assigned to older, and predominantly the oldest age group was attributable to a significantly lower rate of repeated ablations (5%, 13%, 14%, P=0,004). In conclusion, antiarrhythmic drug initiation after complex catheter ablation of atrial fibrillation is a common strategy, advancing with patient's age and improving procedure success by 10% to 15%. With the current rise of complex catheter ablation for atrial fibrillation, we presume that it represents the most popular approach of hybrid therapies. In accordance with the experience of the pharmacological therapy combined with CTI ablation, the majority of indicated patients are elderly and polymorbid individuals, who are more likely to remain on current antiarrhythmic therapy than undergo a repeat procedure when facing a recurrence of arrhythmia.

ATRIOVENTRICULAR (AV) NODE ABLATION AND PERMANENT PACEMAKER – "ABLATE AND PACE STRATEGY"

The induction of atrioventricular conduction block using catheter ablation and subsequent permanent pacing is the oldest non-pharmacologic treatment option for atrial fibrillation. The palliative nature of the procedure is treating a rapid heart rate associated with AF and drug-refractory fast ventricular response, not atrial fibrillation itself. The most com-

mon symptoms are palpitation, shortness of breath and weakness. The "ablate and pace strategy" manages well the patient's subjective symptoms and may stabilise cardiac output in patients with tachycardia-induced cardiomyopathy. However, it does not treat the arrhythmia itself and the AF related risks, mainly risk of cardioembolic stroke, which still present a threat. In most patients, the antiarrhythmic drug therapy can be discontinued and anticoagulant medication remains the first-line treatment.

The first ever AV node catheter ablation using direct current was performed by Scheinman in a patient with highly symptomatic paroxysmal atrial fibrillation on April 9, 1981. The outcome was optimal with no complications reported [44]. During the 1980s, AV node ablation using direct current became commonly used in developed countries for the management of patients with pharmacoresistant supraventricular arrhythmias [45]. Simultaneously, new methods of ablation therapy were researched leading to the introduction of radio-frequency ablation [46, 47]. Radio-frequent energy has proven superior in efficacy, safety and controlled focal delivery and became the most preferred approach in catheter ablation of arrhythmia until today, after DC ablation was abandoned in the late 1980s [48].

With the development of selective catheter ablations for a number of supraventricular arrhythmias, the procedure is now strictly reserved for the treatment of certain types of atrial fibrillation [49].

Ablation of a compact AV node, being currently a standard radio-frequency ablation procedure, has almost a 100% success rate, has a short duration and presents very few complications [50, 51]. Patients have permanent pacemakers implanted which are programmed to rate responsive VVI,R mode (adjusting rate according to the physiologic needs of the patient).

Despite the fact that AV junction ablation itself is a simple and safe procedure, "ablate and pace" strategy is associated with many risks. High incidence of sudden death and ventricular tachycardias torsade de pointes and ventricular fibrillation has been reported within the first few months after AV junction ablation. The risk of 2.1 to 6% [52, 53] is attributed to a prolonged QT interval and repolarisation abnormalities mediated by bradycardia in patients predisposed to malignant arrhythmias. The risks can be prevented by temporarily setting post-ablation pacing at 80-90 beats/min for one to three months [53].

Moreover, the detrimental effects of long-term right ventricular pacing have been documented, including dyssynchrony, LV remodeling, impairment of the LV ejection fraction, LV dilatation and hypertrophy, and low exercise performance [54]. Critical evaluation of several studies on the effect of single and dual-chamber pacing in the management of bradyarrhythmias has shown deterioration in cardiac output and heart failure symptoms after long-term right ventricular pacing [55]. However, in patients undergoing ablate and pace procedure, the effect was not so disturbing. Topse *et al.* [56] studied a cohort of 55 patients with chronic atrial fibrillation and preserved LV systolic function who underwent ablate and pace treatment. The observations were in line with previous results, a decline in left ventricle function and lower exercise capacity was reported – 49% of patients developed left ventricle dyssynchrony detected by echocardiography. In these patients NYHA functional class increased from 1.8 to 2.2, left ventricle ejection fraction decreased from 48% to 43% and left ventricle end-diastolic volume increased from 116 to 130 ml. Yet, the findings have proven statistically significant with a P-value < 0.05. The remainder of patients did not report any change in cardiac function.

The evaluation of a non-randomised group of patients treated with AV node ablation and permanent pacemaker implant has shown a clear benefit of this therapeutic strategy. The APT trial [51], prospectively assessing quality of life, survival, exercise capacity and ventricular function in 156 patients within 12 months of AV node ablation for atrial fibrillation, has proved moderate improvement in left ventricular function, mostly exhibited in patients with severe left ventricular dysfunction at baseline reporting increase in LV ejection fraction from 31% to 41%. All patients demonstrated NYHA functional class improvement from 2.1 to 1.8 and noted significant improvement in quality of life. As compared to the aforementioned study, the absence of adverse effects of long-term right ventricular pacing can be easily explained by the fact that the beneficial effect of optimal rate control in tachycardia-induced cardiomyopathy prevailed the negative influence of right ventricular pacing. Wood *et al.* conducted a review of 21 clinical studies on AV nodal ablation and permanent pacemaker implantation in patients with drug-refractory atrial fibrillation, published between 1989 and 1997. Of the 1,181 documented patients, all parameters - quality of life, ventricle function, exercise tolerance or required medical treatment - have improved significantly [57].

In comparison with the conventional drug therapy, the ablate and pace strategy manifested similarly promising results. The AIRCRAFT trial followed a cohort of 63 patients randomised to pharmacologic and ablate and pace therapy for five years and showed no statistical difference in ejection fraction parameters or survival analysis between the treatment groups. The patients undergoing AV node ablation and permanent pacemaker implantation demonstrated a significantly better quality of life with fewer symptoms [58].

Long-term survival of the patients receiving ablate and pace therapy was studied by Ozcan *et al.* [59]. All patients undergoing AV nodal ablation and subsequent permanent pacemaker implantation for atrial fibrillation at Mayo Clinic between 1990 and 1998 were included into the analysis. Observed survival rates were compared with two control populations: matched population of Minnesota, USA and a group of consecutive patients with atrial fibrillation who received drug therapy in 1993. At 36 ± 26 months of follow-up, survival among patients with atrial fibrillation showed no differences whether they received ablation or drug therapy and was significantly lower than the survival rates in the general population of healthy adults, (see Fig. **3**).

As the available data demonstrate, ablate and pace strategy provided a substantial decline in symptoms and improvement in quality of life as compared to pharmacologic therapy, while there was no clinically relevant evidence of adverse effect on cardiac output and associated heart failure

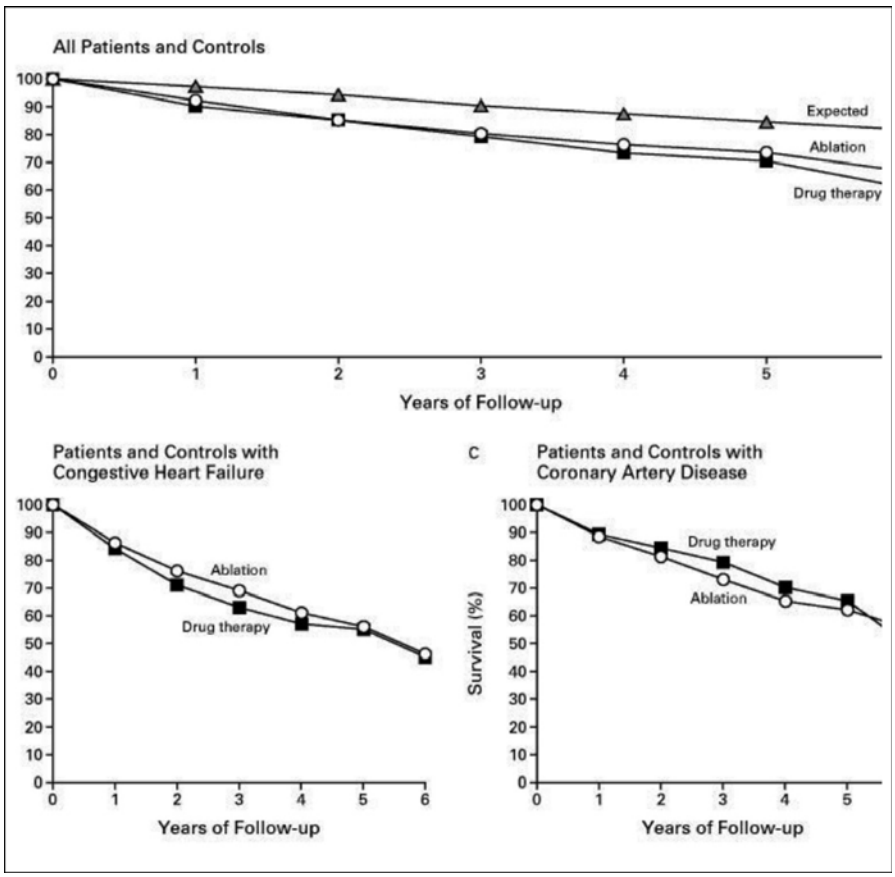


Fig. (3). Observed survival among patients who underwent ablation of the atrioventricular node and among controls treated with drugs for atrial fibrillation, and expected survival rates based on mortality in an age- and sex-matched general population. As shown in Panel A, observed survival among patients who underwent ablation of the atrioventricular node and implantation of a permanent pacemaker for atrial fibrillation between 1990 and 1998 was worse than the expected survival based on mortality among age- and sex-matched members of the Minnesota population (P<0.001); however, it was similar to the survival among controls treated with drugs for atrial fibrillation (P=0.44). In the subgroup of patients with congestive heart failure (Panel B), the survival among the 115 patients who underwent ablation was similar to that among the 58 controls treated with drugs (P=0.75). In the subgroup with coronary artery disease (Panel C), the survival rates were not significantly different for the 156 patients who underwent ablation and the 83 controls treated with drugs (P=0.85). Courtesy of Ozcan *et al*., 2001 [59].

symptoms, morbidity and mortality of the patients. This inconsistency is mainly caused by the prevalence of beneficial effects of rate control, discontinuation of antiarrhythmic drug therapy with side effects and proarrhythmic potential and positive impact on tachycardia-induced cardiomyopathy against the adverse effects of chronic right ventricular pacing on LV functions in some patients.

In 2005, Doshi *et al.* [60] published data from the PAVE study, the first trial comparing the effects of chronic biventricular pacing to right ventricular pacing. They randomly assigned 184 patients with chronic atrial fibrillation, in whom ablate and pace procedure was successfully performed, to receive either a right ventricular apical pacing or a biventricular pacing device. During a follow-up period of six months, a six-minute corridor walk test, quality of life and left ventricular functional status were observed. Both the treatment groups demonstrated improvement in all categories. While the quality-of-life score showed no difference with biventricular pacing or right ventricular pacing, there was a significant increase in exercise tolerance (31% to 24% increase in six-minute corridor walk distance, P=0.04) and ejection fraction (46% to 41%, P=0.03) in the biventricular group. Patients with left ventricular ejection fraction ≤ 45% or heart failure symptoms expressed by NYHA class II-III at baseline profited more from biventricular pacing in comparison with the patients who did not have reduced ejection fraction or heart failure (NYHA I) prior to device implantation.

In 2011, Brignole *et al.* [61] reported a study of 186 patients randomised to chronic right ventricular apical pacing (RV) or optimised echo-guided biventricular pacing (CRT) after undergoing ablation of AV junction. A primary composite endpoint of death from heart failure, hospitalization due to heart failure or worsening HF were observed during a follow-up of 20 months. The CRT group showed significantly better results compared to the RV group (11% to 26%, P=0.005). Total mortality was similar in both treatment groups. The beneficial effect was consistent in patients who met the standard indication criteria for biventricular pacemaker implantation (EF ≤ 35%, NYHA Class ≥ III and QRS width ≥ 120) as well as for those who did not. Biventricular pacing proved superior to right ventricular pacing in reducing manifestation and progression of heart failure in patients undergoing ablate and pace therapy for management of atrial fibrillation, (see Fig. **4**).

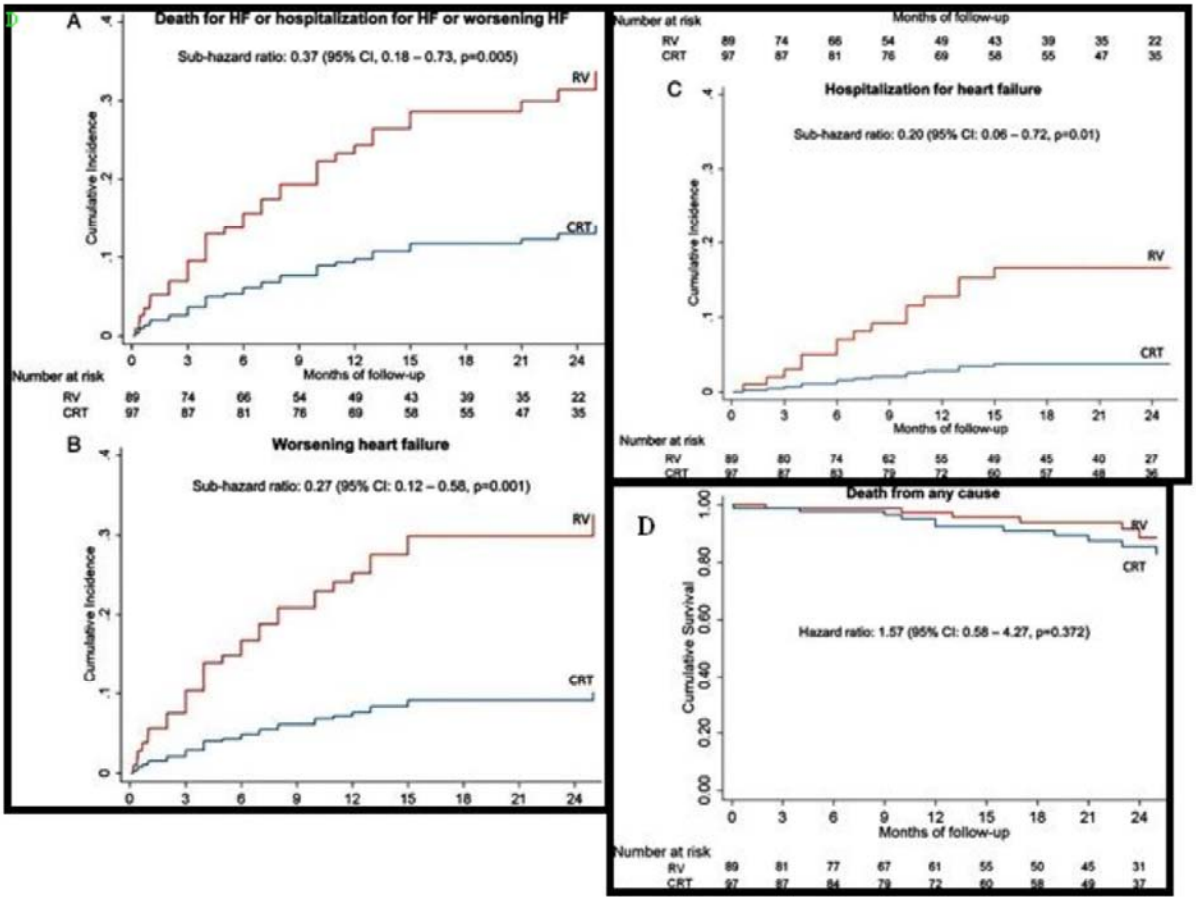


Fig. (4). Clinical endpoints. (A) Corrected cumulative incidence of the composite outcome of death from heart failure, hospitalization due to heart failure, or worsening heart failure ('clinical failure') (primary outcome). (B) Corrected cumulative incidence of worsening heart failure. (C) Corrected cumulative incidence of hospitalization for heart failure. (D) Kaplan–Meier estimates of the probability of death from any cause. HF = heart failure. Courtesy of Brignole *et al*., 2011 [61].

These findings were in conformity with the meta-analysis involving five randomised clinical trials assessing optimal pacing modality (RV or CRT) after AV nodal ablation in a total of 686 patients [62]. Biventricular pacing was attributed to a non-significant reduction in mortality, but a significant reduction in heart failure-related hospitalization and an increase in left ventricular ejection fraction. Meanwhile, both groups were similar in quality-of-life parameters and the six-minute walk test.

A clear superiority of ablate and pace therapy with biventricular pacing to conventional pharmacologic treatment aims to define the AVERT-AF trial [63]. This prospective, double-blinded, multicentre trial will randomise the patients with atrial fibrillation and depressed ejection fraction to either AV node ablation with subsequent biventricular pacemaker implantation or pharmacologic therapy. The tested hypothesis is that biventricular pacing, regardless of heart rate or QRS duration, significantly improves exercise capacity and functional status of the patient in comparison with drug therapy. The results are highly anticipated.

Although the ablate and pace strategy has a history of more than 30 years and seems now to be outdated when compared to the complex catheter ablation in the left atrium, it still has its place in the management of atrial fibrillation. The technique of AV junction ablation has been mastered and the risk for occurrence of early ventricular arrhythmias and sudden death can be prevented by optimal pacemaker programming. Multiple studies have shown that this therapeutic option provides a reduction in symptoms of atrial fibrillation with rapid ventricular response while preventing an increase in mortality and substantial deterioration in left ventricular function. With implantation of the biventricular pacing system, predominantly in patients with impaired left ventricular function, the ablate and pace strategy is superior to conventional pharmacology therapy.

Being generally less demanding, this alternative therapy is reasonable in patients with persistent or chronic atrial fibrillation and pharmacologic-resistant rapid ventricular response who are unable or unwilling to undergo curative complex catheter ablation. Polymorbid elderly patients or patients concerned about the high risk of recurrence and re-ablation after initial complex catheter ablation are the target population. Indication of this method for patients with paroxysmal atrial fibrillation is rare. In conformity with ACC/AHA/HRS Atrial Fibrillation Practice Guidelines [64], patients with normal ventricular function or a reversible decline in ventricular performance requiring AV nodal ablation are recommended for right ventricular pacing device implantation. Indication for biventricular pacing system is now lim-

ited to patients with pre-existing impairment of left ventricular function not mediated by uncontrolled tachycardia. In patients with implanted right ventricular pacemaker subjected to AV node ablation, the upgrade to biventricular pacing device is recommended.

ATRIAL PACING IN COMBINATION WITH ANTIARRHYTHMIC MEDICATION

It has been known for many decades that atrial pacing reduces the risk of the onset of atrial fibrillation and does so by affecting both the triggering factors of AF and the atrial substrate itself. Premature atrial beats can induce arrhythmia in predisposed individuals in several ways. In most cases, premature impulses responsible for arrhythmia triggering have a short coupling interval, but AF may also be preceded by a sinus pause or short-long-short interval sequence [65]. The key element for reentry initiation is the anatomical substrate of atria, particularly dispersion of conduction and refractoriness in various areas of the left and right atrium [66]. Atrial pacing has the ability to positively influence these factors, thus it had been presumed that atrial pacing would demonstrate a protective effect against progression of persistent AF in comparison to ventricular pacing, and the premise was proven true in the late 1980s. After a follow-up period of two years, only 6.7% patients with AAI pacing developed atrial fibrillation as compared to 47% of patients with VVI pacing, $P < 0.0005$ [67]. Unfortunately, further research has not met expectations and the proposed benefit has been definitely disproved by PA3 STUDY, a randomised crossover comparison of DDD and VDD pacing for prevention of atrial fibrillation in patients with paroxysmal AF referred to catheter ablation of AV node and permanent pacemaker implantation. The hypothesis that unlike ventricular (VDD) pacing, atrial pacing in DDD mode will prevent arrhythmia recurrence and impede the progression of paroxysmal AF to its persistent form was not confirmed and no significant difference between the treatment groups was found [68].

In order to affect triggers of AF, a multitude of preventive pacing therapies designed to achieve stabilised atrial rhythm and prevent premature atrial impulses has emerged during the 1990s. Despite many efforts, the beneficial effect of most of these algorithms was inconsistent and did not reach statistical significance in preventing AF [69, 70].

Alongside the attempts to eliminate triggering factors, modalities to alter anatomical substrate have also been examined. Several studies both in animal models and humans have suggested conduction delays and inhomogenities in the dispersion of conduction and refractoriness resulting in intra- and interatrial asynchrony to be of great importance [66, 71, 72]. Thus, it was assumed that unconventional single or multi-site atrial pacing in patients exhibiting these conditions would homogenise atrial conduction, reduce conduction delay of the areas beyond the activation time sequence and alleviate atrial asynchrony.

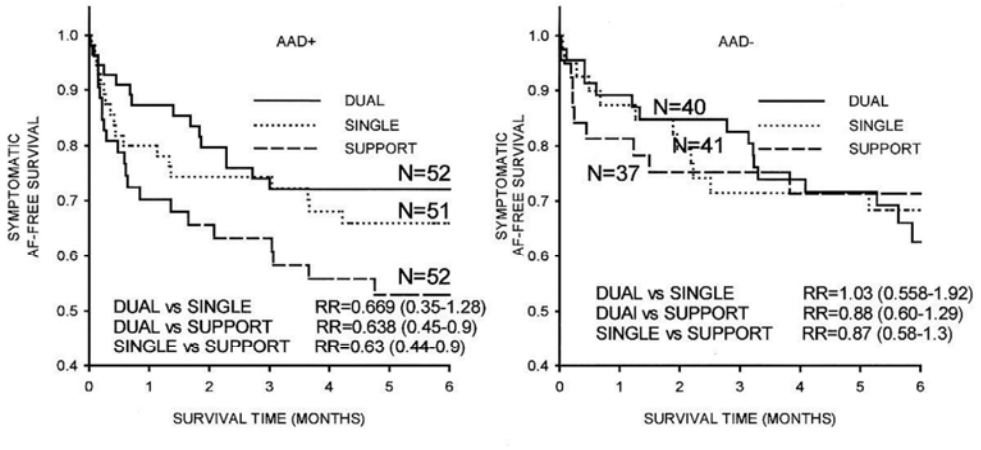
During the 1990s, three different preventive pacing modes were introduced. Biatrial pacing (stimulation from both the right and the left atrium) was tested by D'Allonnes *et al.* In a prospective study, 64% of patients with atrial tachyarrhythmias and prolonged P-wave receiving biatrial pacing remained in sinus rhythm after 33 months of a mean follow-up [73]. However, maintenance of sinus rhythm was mostly achieved by previously ineffective antiarrhythmic drug therapy. Dual-site pacing (simultaneous pacing from two different sites of the right atrium – high right atrium and coronary sinus ostium) was developed by Saksena *et al.* [74].

The study showed a clinically significant difference in the incidence of AF episodes before and after implantation, but the superiority of either dual-site or single-site pacing has not been proven. The next larger prospective crossover study comparing 118 patients with dual-site, single-site and support (VDI, DDI) atrial pacing for paroxysmal atrial fibrillation revealed nothing more than a trend towards prolongation of arrhythmia-free intervals in patients with dual-site pacing and only in those with parallel antiarrhythmic therapy [75], see (Fig. **5**).

Decreased incidence of newly onset atrial fibrillation achieved with pacing of the triangle of Koch has been proved by Papageorgiou [76]. Another study comparing alternative interatrial septum pacing at the triangle of Koch with standard right atrial pacing has proved that both pacing modalities were effective in preventing a recurrence of atrial fibrillation while patients remained on previously ineffective antiarrhythmic treatment; the difference was significantly higher in interatrial septum pacing arm [77]. The overall results of pacing therapy for paroxysmal AF, including various protocols and designs, were inconsistent and disputable. None of the preventive algorithms have indicated a clear clinical benefit. Therapeutical pacing modalities (biatrial, dual-site pacing or stimulation at the triangle of Koch) proved superior to conventional pacing, although it was not powered enough to yield clinical implication as a first-line treatment for atrial fibrillation. The methods have remained a substitute strategy for patients with paroxysmal AF who are indicated for permanent pacemaker implantation, in whom they may reduce the risk for recurrent arrhythmia. However, due to many constraints and complication risks associated with pacing from atypical sites of both right and left atrium, the method became obsolete and unused.

IMPLANTABLE ATRIAL DEFIBRILLATOR IN COMBINATION WITH ANTIARRHYTHMIC MEDICATION

As the last but not least device-based therapy for atrial fibrillation, implantable defibrillator (atrioverter) was presented. The device has the ability to detect and terminate an episode of AF shortly after the initiation. Reflecting the fact that one half of the episodes are accompanied by atrial tachyarrhythmias [78], defibrillators are equipped with a multitude of antitachycardia pacing algorithms (burst, ramp, high frequency pacing) and in case of failure, arrhythmia is terminated by cardioversion shocks synchronised on R-wave sensing with low energy delivery. Parallel antiarrhythmic drug regimen is present in most patients and may enhance the efficacy of cardioversion, reduce early recurrence of AF and decrease the number of cardioversion shocks and thus eliminate shock-related inconvenience. Implantation of an atrial defibrillator may be reasonable in preventing arrhythmia episodes, but also the incidence of newly onset atrial fibrillation. Wijffelse *et al.* suggested that the concept of "atrial fibrillation begets atrial fibrillation" [79] implicating early



	Paired Wilcoxon sign test			Paired Wilcoxon sign test
Dual vs Single, (n=19)	p=0.064		Dual vs Single, (n=16)	p=1.000
Dual vs Support, (n=23)	p=0.011		Dual vs Support, (n=15)	p=1.000
Single vs Support, (n=25)	p=0.108		Single vs Support, (n=12)	p=1.000

Fig. (5). Freedom from all symptomatic atrial fibrillation (AF) in each randomized pacing mode in study population receiving concomitant class 1 or 3 antiarrhythmic drugs (AAD+ on the left) or without concomitant drug therapy (AAD− on the right). Dual right atrial (RA) pacing but not high RA pacing shows prolongation of time interval to AF recurrence as compared with support pacing and a trend to prolongation as compared with high RA pacing in drug-treated patients. There is no difference in outcome in patients on any randomized pacing mode without concomitant drug therapy. AAD = antiarrhythmic drug. Courtesy of Saksena *et al*., 2002 [75].

treatment of recurrent AF may lead to preventing the progress of arrhythmia. During the 1990s, some centres performed a single chamber atrial defibrillators implantation in patients with paroxysmal atrial fibrillation. In spite of promising results for terminating the episodes of AF [80] (nearly 100% of episodes of atrial tachyarrhythmias were converted to sinus rhythm), the device implanted was not widely accepted. The reason for dispreference was presumably the financial burden of the therapy, potential risks and questionable cost-benefit ratio for non-life-threatening arrhythmias. Additionally, electric shock therapy even with low energy output of 2-6 J will cause discomfort to the patient and in cases of non-life-threatening arrhythmias with no presence of underlying comorbidities, the shock delivery was often disabled. Geller *et al.* [81] has published a long-term follow-up of 106 patients with drug-refractory atrial fibrillation treated with an implantable atrial device and pharmacologic therapy. Only 39 patients were actively receiving a combined therapy. In the remainder of 63% patients, the device was used to monitor the arrhythmia (14 patients) or was turned off or explanted (53 patients). On the other hand, dual chamber defibrillators are able to recognise and treat not only malignant ventricular arrhythmias, but also atrial tachyarrhythmias in a similar fashion as mentioned previously. Efficacy for successfully treating atrial episodes is high and the minority of devices are turned off or explanted with respect to parallel management of serious, life-threatening ventricular arrhythmias [82]. In 2006, a TRADE HF trial was initiated to evaluate the outcome of automatical electric therapy delivered by dual chamber defibrillators for the treatment of atrial tachyarrhythmias in patients with heart failure who are subjected to biventricular defibrillator implantation [83]. This prospective, randomised, open-label trial is assessing the effect of device-based therapy on morbidity and mortality of patients who are at risk for atrial tachyarrhythmias. The results are not yet available.

Atrial defibrillator implantation does not succeed as a reasonable therapy for atrial fibrillation and is not currently used. In contrast, dual defibrillators are indicated to a subgroup of patients with different characteristics. The final verification of the method has yet to be fully explored by the ongoing studies.

FUTURE DIRECTIONS

Today, most of the strategies mentioned above have been rendered obsolete and are limited to a small number of patients. The idea of hybrid therapy itself represents a very broad and universal concept and includes a variety of therapeutic options. Indication for medical therapy is sub-optimal and restricted and new hybrid approaches are sought. As left atrial catheter ablation based on pulmonary vein isolation (PVI) has proven efficient, further refinement of complex interventions in the left atrium and combination with other methods are being explored.

Recently, catheter-based renal denervation hit the spotlight of novel approaches. The procedure aims at denervation of renal artery sympathetic nerves resulting in decreased sympathetic tone with all the beneficial effects related to inhibition of the overdrive in renin-angiotensin-aldosterone system. Most of the study protocols are designed with a focus on refractory hypertension, but as research data suggest,

also arrhythmias, including atrial fibrillation, may be affected. The first study published by Pokushalov *et al.* [84] involved 27 patients randomised to PVI only or PVI with catheter-based renal denervation. In patients treated with renal devervation, a significant reduction in blood pressure (181 ± 7 to 156 ± 5, $p < 0.001$ measured for systolic BP, 97 ± 6 to 87 ± 4, $p < 0.001$ for diastolic BP) as well as improvement in the proportion of arrhythmia-free patients was observed (69% to 29%, P=0.033). However, the findings require further validation in larger, randomised, preferably double-blinded trials.

In an effort to maximalise the effect of the procedure, two complementary, but differently approached techniques for radio-frequency ablation are being combined: minimally invasive epicardial ablation and conventional endocardial catheter ablation. The interventions can be performed in a single procedure at the hybrid operating room, or in stages with inter-procedural time interval being days or weeks. Although convergent ablation does not meet the presumption of combining two different therapeutical approaches as both interventions are based on creating a set of circular and linear lesions, such a distinctive methodology allows classification of hybrid ablation. In terms of efficacy, the procedures as stand-alone therapy are comparable and limited. The success rate of catheter ablation for paroxysmal fibrillation exceeds 80% [85] and epicardial mini-thoracotomy ablation is equally effective [86].

A literature review reveals a variety of the surgical procedures varying in execution of thorascopic epicardial ablations. In May 2012, Zembala *et al.* reported data from 27 patients with persistent and long-standing persistent atrial fibrillation treated with a combined approach of a transdiaphragmatic pericardioscopic surgical ablation and endocardial catheter ablation [87]. The interventions were performed in a staged procedure with a 15 to 20-day interval before readmission. At the six-month follow-up, the sinus rhythm was restored in 72.2% of patients (13/18), 66.5% of patients (12/18) being off antiarrhythmic medication. After a one-year period, sinus rhythm was maintained in 80% of patients (8/10) who remained without medication. Three major adverse events were reported: a case of cardiac tamponade requiring surgical intervention with recurrence after 30 days; a case of laceration of the inferior vena cava with serious bleeding necessitating a sternotomy; and a case of death of unknown cause 27 days after discharge. In the latter case, an autopsy was not performed due to patient's religious beliefs. In January 2013, data from 101 patients undergoing exactly the same intervention were published [88]. Patients with an anticipated lower success rate with endocardial ablation, such as patients with previously failed ablation, patients with persistent atrial fibrillation and left atrial enlargement or patients with long-standing persistent AF, were considered eligible for the convergent ablation. Procedures were performed simultaneously in a hybrid operating room. During the one-year follow-up, 66.3% of patients remained free from arrhythmia after a single procedure and 70.5% of patients remained free from arrhythmia with repeated ablations. Additional ablations were required in 6% of patients and 37% of patients were on concomitant antiarrhythmic medication. Two deaths were encountered: one due to atrioesophageal fistula and the other due to sudden cardiac death with no apparent cause.

A different approach combining endocardial catheter ablation and off-pump thoracoscopic epicardial ablation was introduced by Pison *et al*. [89]. Equipped with a hybrid operating room, the interventions were performed in a single procedure. The study population included 26 consecutive patients, of those only 42% were with persistent AF. At 12-months follow up, a single-procedure success rate was 83% (79% for paroxysmal AF, 90% for persistent AF). Repeated procedures were performed in 9% of patients. Overall procedural success at one-year follow-up, including multiple procedures, was 93% in patients with paroxysmal AF and 90% in patients with persistent AF. No major complications were reported; only one case of pleural effusion and one case of chest pain at the port insertion occurred, see (Fig. **6**).

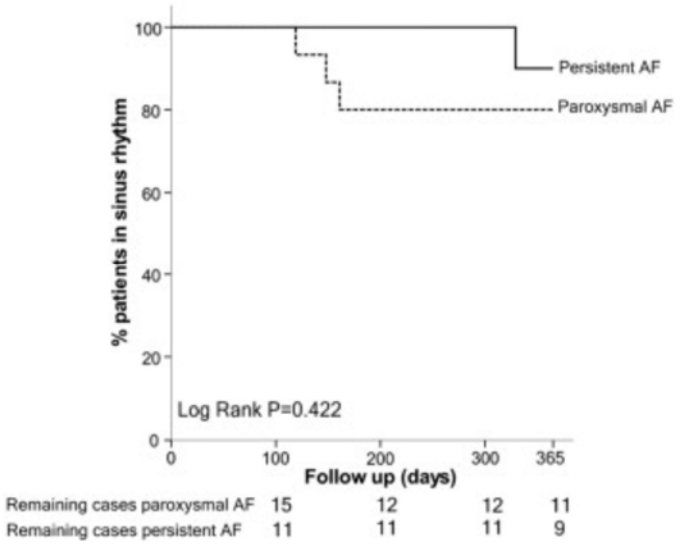


Fig. (6). Kaplan-Meier curve showing the outcomes of hybrid ablation procedures. At 1-year follow-up, hybrid ablation resulted in an overall single-procedure success rate of 83% (79% for paroxysmal atrial fibrillation [AF] and 90% for persistent AF). An event was considered a patient who, at any time after the blanking period, had recurrent supraventricular tachycardia, Courtesy of Pison *et al*. [89].

In 2012, another study on hybrid ablation was published by Muneretti *et al.* [90]. Monolateral thorascopic ablation creating a box lesion and standard catheter ablation after a period of 30 days was performed in patients with persistent and long-standing persistent atrial fibrillation. Additional catheter lesions completing a box lesion formation were required in 61.1% of patients. After a mean follow-up of 30 months, 91.6% of patients remained in sinus rhythm, of whom 77.7% were off antiarrhythmic medication. No procedural complications were documented.

The results of the first two aforementioned trials using a transdiaphragmatic approach were highly controversial. Researchers targeted a specific population of patients with persistent or long-standing persistent atrial fibrillation, in whom management of the arrhythmia is challenging. Nevertheless, the reported success rate was not superior to standard catheter ablation and the occurrence of adverse events was critically high. Three cases of death was alarming, even though two of them have no proven causality. Conversely, data reported by Pison are encouraging and a significant level of proven success with minimum complications proposes further confirmation of the method. Unfortunately, the study participants exhibited mostly paroxysmal AF, which for standard catheter ablation provides a satisfactory outcome. Despite a small population, the method suggests robust, safe and efficient and further evaluation, predominantly in patients with persistent and long-standing AF and left atrial dilation who might profit the most, should follow. Findings published by Munretti *et al.* also suggest eligibility of those patients for convergent ablation, reporting high long-term efficacy. On the basis of the current knowledge, hybrid ablation, especially minimally invasive thorascopic surgeries, indicates useful treatment for otherwise unmanageable patients with persistent and predominantly long-standing persisting AF and left atrial enlargement or concomitant structural heart disease.

Despite its 30-year history, hybrid therapy of atrial fibrillation is still a reasonable, non-pharmacological strategy, even though reserved to limited subgroups of patients. The advanced techniques of hybrid therapy, namely the combination of complex catheter ablation for atrial fibrillation and catheter-based renal denervation or hybrid epicardial and endocardial ablation has the prospect of becoming the treatment of choice in selected patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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