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(Article begins on next page)

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Catheter ablation in atrial fibrillation:

Is there a mortality benefit in diabetics with heart failure?

Mario Matta[1], Andrea Saglietto[2], Paolo De Salvo[2],

Arianna Bissolino[2], Andrea Ballatore[2], Matteo Anselmino[2]

[1]Division of Cardiology, Sant'Andrea Hospital, Vercelli, Italy

[2]Division of Cardiology, Department of Medical Sciences, Città della Salute e della Scienza, University of Turin, Turin, Italy

Running title: AF ablation in HF and DM patients

Corresponding Author:

Matteo Anselmino, MD PhD

Cardiology Division, Department of Medical Sciences

"Città della Salute e della Scienza" Hospital

Corso Bramante 88, 10126 Turin

University of Turin, Italy

email matteo.anselmino@unito.it

phone 00 39 0116709598

fax 00 39 0112369598

Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia, and patients with diabetes mellitus (DM) present an increased incidence of AF. Besides DM, heart failure shares pathophysiological links with AF, mainly related to the pathological remodeling of hearts affected by structural disease. As in a vicious circle, AF may contribute to heart failure worsening and increased mortality in patients with structural heart diseases, and the outcome may be further impaired when concomitant DM is present. Although no data directly referring to DM patients with heart failure are available, indirect information can be drawn from large studies on patients with HF and AF. The present review discusses the outcome of AF ablation in patients with DM and HF, focusing on safety, efficacy and most of all hard endpoints such as mortality and thromboembolic events incidence.

Key words: atrial fibrillation, diabetes, heart failure, catheter ablation, clinical outcome

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, and patients with diabetes mellitus (DM) present an increased incidence of AF [1,2,3]. DM impacts coronary micro- and macrovasculature resulting in left ventricular systolic and diastolic dysfunction, leading to increased incidence of heart failure (HF) and, consequently, atrial structural remodeling [4,5]. Patients with DM present high levels of inflammatory markers [6,7], and chronic inflammation results in accelerated myocyte breakdown and fibrosis [8,9]. Finally, diabetic autonomic neuropathy can increase the risk of AF occurrence [10,11] through the imbalance of the autonomic nervous system, and potentially raises the risk of thromboembolic events [12]. Besides DM, HF shares pathophysiological links with AF, as this arrhythmia is relatively common in patients with HF [13]. Conversely, AF occurrence frequently contributes to HF worsening and increased mortality in patients with structural heart diseases, resulting in a vicious circle of whom the optimal treatment is difficult to identify [14,15].

Catheter ablation is an established treatment option for symptomatic AF [16]. Recent evidences suggest that this procedure is safe and effective even in patients with HF and DM [17,18], providing also long-term survival benefits in HF patients [19]. However, no studies have been performed to specifically address diabetic patients with HF.

The present review aims to discuss the outcome of AF ablation in patients with DM and HF, focusing on safety, efficacy and most hard endpoints such as mortality.

Pathophysiological links between AF, HF and DM

Multiple mechanisms link AF and HF, as disadvantageous remodeling mechanisms occur as compensation in failing hearts [20,21,22]. Electrical, mechanical and metabolic alterations attempt to preserve an adequate cardiac output, resulting in elevation of left ventricular and atrial pressure, dilation, fibrosis, functional mitral regurgitation and autonomic imbalance, favouring AF occurrence and perpetuation.

Conversely, AF can further impair left ventricular function in patients with structural heart disease, due to the fast and irregular rates and the loss in left atrial contraction, resulting in a tachycardia-induced cardiomyopathy and further acceleration of the HF natural history [23,24].

DM patients, instead, present a complex electrical and anatomical atrial substrate, due to the frequent coexistence of comorbid cardiovascular disease, resulting in atrial myocytes alterations [6,25] and potentially higher AF occurrence and recurrences despite rhythm control therapies. Additionally, a sort of "diabetic cardiomyopathy" has been proposed as an entity sharing common features with other structural cardiomyopathies resulting in HF, confirming the important role played by DM [26,27] (Figure 1).

AF ablation in patients with HF

During the last years several studies have been performed to assess the outcome of AF ablation in HF [28,29,30,31,32]. The safety and efficacy of the procedure were similar to that reported among the general population, and an improvement in NYHA class and left ventricular function were consistently found. A large meta-analysis reported a reduction in the proportion of patients presenting an ejection fraction lower than 35% [17]. Additionally, these benefits were maintained over follow-up, being higher in patients maintaining sinus rhythm and in those with a shorter history of AF and HF duration [33].

Concerning quality of life, AF ablation reduced the number and duration of hospitalizations from HF compared to patients not treated by ablation [34]. Another meta-analysis including 17 randomized trials of patients both with and without HF, showed significant benefit in terms of all-cause mortality and hospitalizations for worsening HF in patients with AF and HF treated by catheter ablation compared to those treated by medical therapy [35].

A randomized trial comparing catheter ablation to amiodarone for AF treatment in patients with HF, the AATAC-AF trial, showed a significantly higher efficacy and lower complications for AF ablation [36]; finally, the CASTLE-AF trial [19], reported a significant benefit for AF ablation in terms of hard endpoints such as mortality, stroke incidence and hospitalization for worsening HF compared to medical therapy in patients with AF and HF.

How to treat AF in diabetic patients?

Previous studies showed that DM patients with AF are affected by a worse prognosis than those in sinus rhythm, both concerning quality of life, hospitalizations and mortality [37,38]. Therefore, rhythm control strategies may reduce or negate the long-term effect of AF in DM patients, turning into prognostic positive effects. However, despite limited to small non-randomized studies, higher recurrences after AF cardioversion [39], and lower in vitro and in vivo efficacy of anti-arrhythmic drugs [40,41] have been described in patients with compared to those without DM.

The largest evidence on AF ablation outcome in patients with DM derives from a multicenter meta-analysis, showing that AF ablation is safe, and long-term efficacy rates were favourable, as approximately half of the patients were free from AF following the first procedure, improving to 65% including repeated procedures [18]. Advanced age and higher basal glycated haemoglobin levels have been identified as predictors of AF recurrences: optimal glycaemic control may, therefore, contribute to optimize AF treatment [18,42,43].

However, higher readmission rates have been described for patients with compared to those without DM following AF catheter ablation [44], along with higher incidence of follow-up adverse events [45], even among those with insulin resistance [46]. Additionally, patients with poor glycaemic control or long-term DM history more frequently required aggressive LA substrate modification instead of pulmonary vein isolation alone [47], as already reported for HF patients [48]. These reports support the presence of a peculiar LA substrate in DM patients suffering from AF, warranting careful attention in defining the optimal treatment in this high-risk subset population.

Current evidence on outcome of AF ablation in patients with DM, with or without concomitant HF, is summarized in Table 1.

Diabetic patients with AF and HF

Although no data directly referring to diabetic patients with HF are available, some indirect information can be drawn from large studies on AF ablation (Figure 1).

The CASTLE-AF trial [19] enrolled overall 110 diabetic patients, 30% of the entire population, 43 of whom in the ablation group. The primary endpoint (composite of death and hospitalization for HF) occurred in 19 (44%) patients in the ablation group and in 34 (50%) patients in the medical group, with a slightly higher incidence compared to the unselected study population (28.5% and 44.6% in the ablation and medical therapy group, respectively). Despite the difference between diabetic and non-DM patients was non-significant, HR for death or hospitalization for HF was 1.01 in the first, compared to 0.55 in the latter groups, suggesting a trend towards a minor AF ablation effect within DM patients. In any case, despite the trial was not designed and powered to investigate the outcome in subset populations, and DM patients are a limited amount of the overall population, these data suggest that HF patients with concomitant DM represent a very high-risk population.

Conversely, in the meta-analysis from our group [17] only 12(9-15)% patients were affected by DM; this comorbidity did not relate to incidence of arrhythmic recurrences compared to non-diabetics; however, the limited number of patients and the meta-analytic nature of this data limit the strength of the finding.

Finally, the AATAC-AF trial [36] included 22% and 24% patients affected by DM in the ablation and amiodarone groups, respectively. Of note, DM was one of the predictors of AF recurrences (HR 2.22 at univariate, 1.10 at multivariate analysis, p=0.010). Moreover, DM was the only significant clinical predictor of AF recurrences, along with amiodarone treatment, suggesting the lower efficacy of AF ablation in this subset population. No data however have been provided on mortality in diabetic patients.

Conclusion

Patients with HF and DM represent a high-risk population, in whom AF occurrence may result in even worse outcome despite the most effective treatments. AF ablation in this subset population, in fact, may be affected by a lower efficacy and higher incidence of long-term follow-up complications, resulting in a limited impact on long-term survival. Future studies are warranted to identify the impact of AF ablation on hard endpoints, such as mortality and stroke, in this high-risk population of diabetic patients with HF.

Disclosure

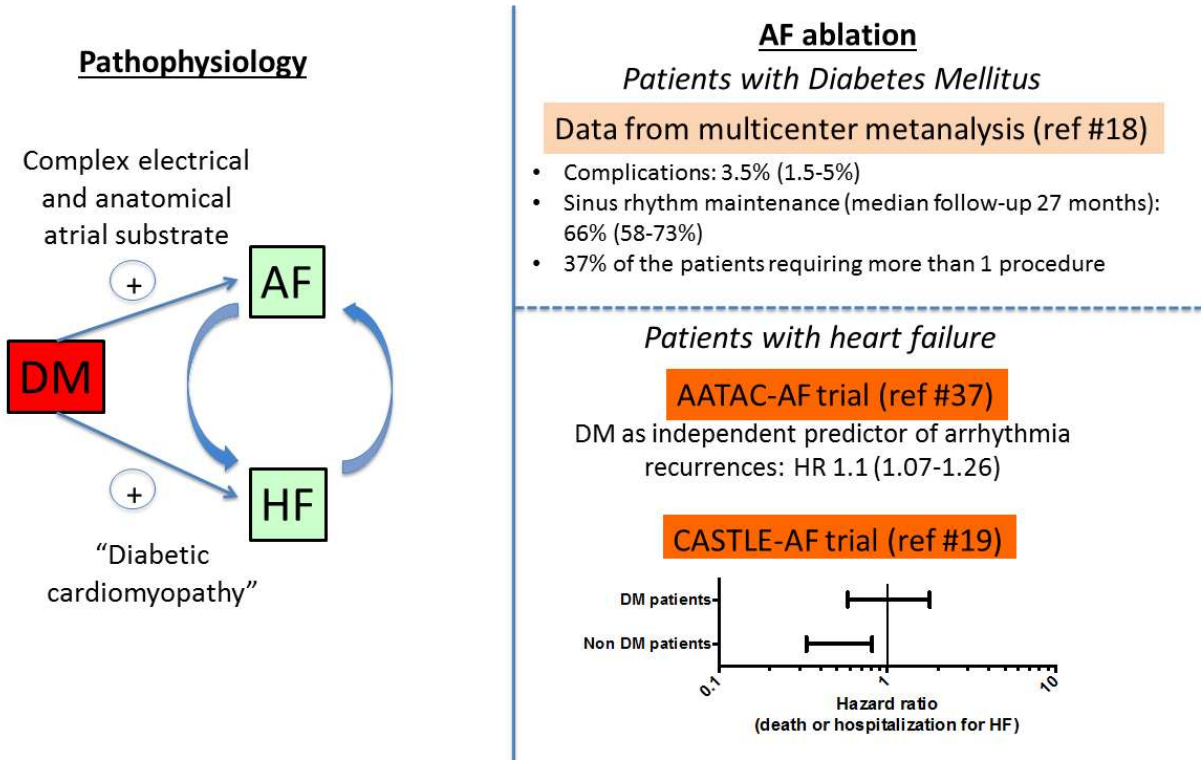
No conflicts of interest.

Table 1. First Author, publication date, population and main characteristics of the studies reporting on AF ablation outcome in diabetic patients.

First Author, Country, Year of Publication	Study design	N. patients	Median follow-up (months)	Paroxysmal AF (%)	Median age (years)	SR at follow-up end (%)
Anselmino, multicenter, 2015 [18]	Meta-analysis	1464	27	65	62	66
Lu, China, 2015 [43]	Retrospective , single center	149	12	100	66	60
Yang, Korea, 2016 [49]	Prospective, single center	142	24	65	63	79
Grieco, Italy, 2018 [47]	Prospective, single center	64	12	100	45	83
Di Biase, USA, 2016 [36]	Randomized, multi center (DM+HF)	22	24	0	62	N/A – higher recurrence
Marrouche, USA, 2018 [19]	Randomized, multi center (DM+HF)	43	38	30	64	N/A – higher mortality/HF

AF: atrial fibrillation. DM: diabetes mellitus. HF: heart failure.

Figure 1. Diabetes mellitus, heart failure and atrial fibrillation. The pathophysiological interaction is presented in the left panel, and the impact of diabetes on atrial fibrillation ablation outcome is reported in the right panel .



AF: atrial fibrillation. DM: diabetes mellitus. HF: heart failure.

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