Atrial fibrillation: a serious public health issue

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Abstract

In the last 20 years atrial fibrillation (AF) has become one of the most important public health issues. Its prevalence (2%) is double than that reported at the end of the last decade and it increases with aging. AF occurs more frequently in males than in females with a ratio of 1.2:1. The incidence of AF ranges between 0.21 and 0.9 per 1000 person/years. The most frequent form of AF is permanent AF that occurs in approximately 50% of patients while the paroxysmal and the persistent forms occur approximately in 25% of patients each. AF is frequently associated with cardiac diseases and comorbidities. The commonest concomitant diseases are: coronary artery disease, valvular heart disease and cardiomyopathies. The commonest comorbidities are: hypertension, diabetes, heart failure, chronic obstructive pulmonary disease, renal failure, stroke and cognitive disturbances. Paroxysmal AF occurs in younger patients and in contrast with the persistent and the permanent forms is associated with a reduced burden of both cardiac diseases and comorbidities. Generally, the history of AF is long lasting, characterized by the progression from the paroxysmal to the permanent form, burdened by frequent recurrences and disturbing symptoms. Patients with AF have a risk of stroke and death 5 fold and 2 fold higher than normal people respectively. In the real world, patients with AF are still undertreated with oral anticoagulants and in a discrete percentage of cases assigned to inappropriate antiarrhythmic strategy or treated with inadequate specific antiarrhythmic drugs. AF management is costly; expenditure per patient/per year is significantly different in different countries. Efforts to improve the implementations of Guidelines recommendations are needed to improve furtherly the quality of care.

Key words: ATRIAL FIBRILLATION / prevalence
PUBLIC HEALTH / incidence
ATRIAL FIBRILLATION / epidemiology

Introduction

In the last two decades, atrial fibrillation (AF) has become one of the most important public health issues and one of the most important causes of healthcare expenditure in western countries. This is mainly due to the aging population and to the increasing prevalence of chronic diseases. Even if AF is not a life-threatening arrhythmia, it significantly influences the quality of life as a result of anatomic, hemodynamic and hemocoagulative consequences. In addition, AF is frequently associated with disturbing symptoms and important socio-economic problems such as permanent disability, cognitive disturbances, hospitalizations and absence from work [1]. Therefore it is crucial to have an updated picture of the epidemiological, clinical and social impact of AF to plan appropriate interventions and adequately allocate human and economic resources.

Search strategy

A systematic review of the studies on atrial fibrillation was performed using the PubMed and EMBASE databases. The search terms used for the analysis included: "atrial fibrillation", "atrial tachyarrhythmias", "epidemiology", "burden", "rhythm control strategy", "rate control strategy", "stroke", "heart failure", "outcome", "cardioversion of atrial fibrillation", "anticoagulant therapy", "antiplatelet agents", "antiarrhythmic therapy", and "radiofrequency catheter ablation". Studies published from 2005 to 2014 with a pre-especified protocol (e.g.: ascertainment of atrial fibrillation, clinical assessment of patients, assessment of "*rate or rhythm control*" strategies, treatment therapies, follow-up of patients subgroups) and analyzing the epidemiological and clinical issues exclusively in the general population were considered. Only when data regarding specific AF issues were scarce or ab-

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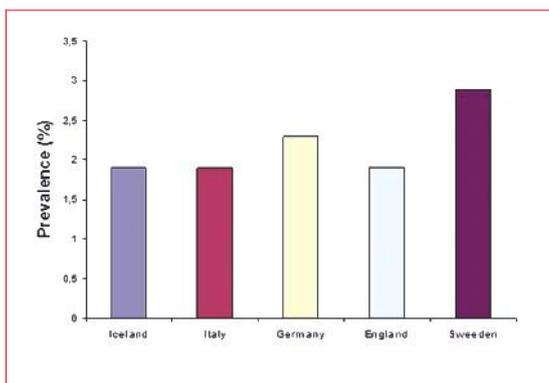
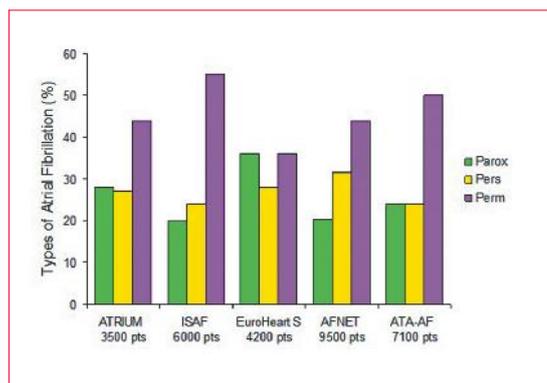**Figura 1**. Prevalence of atrial fibrillation

Figura 2. Distribution of the different types of atrial fibrillation in the real world

sent investigations performed before 2005 were used.

Epidemiology of AF

In Western countries, the prevalence of AF has grown significantly as compared to that reported (about 1%) only one decade ago. Currently, among the general adult population ($\geq$ 15 years old) the prevalence of AF varies from 1.8% in England, 1.9% in Italy and Iceland to 2.3% in Germany and 2.9% in Sweden (Fig. 1). Very likely, this rate is still underestimated due to the presence of a discrete number (10-15%) of asymptomatic forms that remain unknown until the occurrence of the first significant complication (these are also the patients with the worst prognosis) [2-6]. With an average annual growth of 0.04%-0.05% in the general population (data observed from 1998 to 2008 in Iceland and from 1994 to 2012 in England) [2,3] the prevalence of AF is expected to rise to 2.5%-2.6% over the next 15 years [7]. The most probable explanation for this phenomenon lies in the greater ability of treating chronic cardiac/non-cardiac diseases and recognizing patients with AF (greater awareness of the general practitioners, particular attention to identifying subjects with asymptomatic AF) and in the progressive aging of the population. In fact, the prevalence of AF increases with the natural aging process of myocardial tissue (fibro adipose degeneration) and the concomitant growing presence of comorbidities. AF is present in 0.12%-0.16% of subjects aged < 49 years, in 3.7%-4.2% of those aged 60-70 years and in 10%-17% of those aged 80 years or older. In particular, although it manifests more frequently in males than in females (at a ratio of 1.2:1), the female gender represents the majority of cases due to its greater longevity [4,8-13]. Less information is available on the incidence of AF. The most recent studies performed on the global population

report a rate of 0.23, 0.41 and 0.9 new cases per 1.000 person/years in Iceland, Germany and Scotland respectively [3,5,14]. The incidence seems not changing significantly over the time; among USA beneficiaries aged 65 years or older, it varies from 27.3 per 1000 person/years in 1993 and 28.3 per 1000 person/years in 2007. Also the incidence of AF increases with age. In Scotland and in Germany in the subgroup of subjects aged 65-74 years new cases of AF occur in 3.2 and 10.8 person/years respectively, and in 6.2 and 16.8 among those aged 75-84 years [5,14,14a].

The most frequent form of AF is permanent AF, which represents 40-50% of cases, while paroxysmal and persistent forms occur at almost equal rates (20-30% each) in the remaining (Fig 2) [4,8-10,12]. Generally, the history of AF is long and characterized by frequent recurrences. In a study performed in France, the screened patients presented with an average duration of AF of 47 ± 63 months [11]; in the ISAF study in Italy, the history of AF at the time of the screening was < 1 year in only 13% of cases, between 1 and 5 years in 40%, and > 5 years in the remaining 47% [4]. About one-fifth of AF patients suffer from $\geq$ 2 recurrences during the year preceding the screening, and about three-fourths during the previous 5 years [4,10-12]. Despite proper treatment, AF is associated with very uncomfortable or even disabling symptoms in a large percentage of cases. The most frequent reported symptoms are: palpitations in 42%-55% of cases, asthenia in 15%-49%, dyspnea in 24%-49% and angina in 10%-20%. Only 12%-25% of AF patients adequately treated are completely asymptomatic [4,8,10,11]. Patients with permanent AF suffer most often from dyspnea, asthenia and reduced work capacity; those with the paroxysmal form generally from palpitations [1,10,11,15]. The high frequency of recurrences, symptoms and clinical sequelae (stroke, heart failure, need to use anti-arrhythmic drugs, complications related to the

Tabla 1. Heart diseases and comorbidities associated with atrial fibrillation

Study	ISAF [4]	ATA-AF [12]	Euro Heart S [9]	AFNET [8]	ATRIUM [10]
IHD (%)	19	20	34	28	35
Valv Dis (%)	12	33	26	36	/
Dilated CMP (%)	6	13	2	6	/
Hypertension (%)	67	75	63	68	83
Diabetes (%)	23	24	18	22	35
COPD (%)	18	18	13	11	/
Renal Failure (%)	28	19	7	12	20
Heart Failure (%)	25	28	28	36	43
Stroke-TIA (%)	17	15	13	11	18
Cogn Def (%)	15	10	/	/	/

CMP: cardiomyopathy; Cogn Def: cognitive deficiencies; COPD: chronic obstructive pulmonary disease; IHD: ischemic heart disease; TIA: transient ischemic attacks; Valv Dis: valvular disease

use of anti-arrhythmic drugs, etc.) leads to a high rate of hospital admissions [15,16]. In Italy, AF is the cause of 1.5% of all admissions to the emergency rooms; in Germany, the average annual number of hospitalizations for AF is 0.24 per patient and the average number of visits 5.62; in Scotland, the average number of contacts with the General Practitioner (GP) due to AF is 8 per 1,000 person/years. In the USA, in 1999, about 1.38 million of beds were occupied by patients hospitalized with a main diagnosis of AF; a number of beds corresponding to those needed to treat all other arrhythmias combined [5,14,17,18].

AF is generally associated with different forms of heart disease and with multiple comorbidities. Myocardial hypertrophy, ischemic heart disease and valvular heart disease are the cardiac abnormalities mainly associated with AF, while hypertension, diabetes, renal failure, chronic obstructive pulmonary disease, cognitive deficiencies and cerebrovascular diseases the commonest comorbidities (Tab. 1). Three or more comorbidities in combination are present in about one-third of cases [4,8-10,19]. The so-called "lone AF" (AF in the absence of heart disease and/or comorbidity) is found in a low percentage of cases that varies from 2% to 12%. Unlike subjects with permanent AF, subjects with paroxysmal AF are generally younger and with a lower frequency of heart disease and comorbidity [4,8-12,14].

The different forms of AF are associated with different patient profiles and clinical outcomes which are often influenced by how early is the diagnosis and how early is the decision to initiate an adequate therapy. In fact, many studies have shown that the clinical setting of AF is an evolving picture that develops over time, generally beginning with the paroxysmal form and ending with the permanent form, following a timeline that depends on numerous clinical factors [7]. From these studies, it appears that the progression is characterized by a peak, which coincides with the first year after the initial episode, followed by a continuous "crescendo" that depends on the patient's clinical profile, the location where treatment is administered (community, in-hospital ward) and the characteristics of the physician who manages the patient (cardiologist, internist, GP). During the first year, the progression to the permanent form can be observed in about 4% of cases if the patient is managed by a specialist in arrhythmology and in 9% if the patient is treated by a GP or by an internist; at five years, in 18% and 25% respectively. In particular, progression is related to: age, left atrial dimension, not use of anti-arrhythmic drugs, presence of valvular disease or heart failure, arterial hypertension, obstructive pulmonary disease, and use of VVI cardiac pacing [20-24].

Prognosis of patients with AF

AF is associated with an increased risk of stroke (ischemic), hemorrhagic complications (secondary to the associated anticoagulation therapy), hemodynamic consequences and death. Cognitive deficits, heart failure and socio-economic problems are furt-

her serious clinical consequences of AF. It is estimated that among the general population more than one-fifth of all strokes can be related to AF; this rate increases to one-fourth if patients are aged 80 years or older. Subjects with AF show a risk of ischemic stroke five times higher than the normal population, irrespective of the type of AF [25-27]. However, the risk of the ischemic stroke is reduced dramatically with the systematic use of oral anticoagulants (OAC). In the USA, among subjects with AF aged 65 years or older, the significant increase in the use of OAC has led to a drop of the rate of ischemic stroke from 48 per 1.000 person/years in 1992 to 17 per 1.000 person/years in 2007; in Sweden, in the general population the rate of ischemic stroke is 25 per 1.000 person/years among patients treated with OAC and 45 per 1.000 person/years among those not treated. Notwithstanding the significant increase of antithrombotic treatment, in the same countries and in the same periods the risk of the hemorrhagic strokes has remained unchanged over time, maintaining a rate of 2 cases per 1.000 person/years [28,29]. Ischemic stroke is generally more serious and often associated with serious disability; this is probably due to anatomical reasons and to the presence of intercurrent coagulation disorders: 1) the thrombus affects more easily the anterior cerebral circulation, 2) often the clot is not unique and sometimes it shatters producing pluri focal lesions, and 3) the acute event is often associated with conditions of general hypercoagulability [16]. As previously mentioned, patients with AF present a rate of cognitive dysfunction (approximately one-sixth of cases) twice higher than in the general population, even in the absence of a history of overt cerebral ischemic attacks. Very likely, this is due to asymptomatic cerebral micro emboli that can be observed in a discrete percentage of cases as small and diffuse cerebral infarct lesions [30,31].

AF is often associated with heart failure (22%-42% of cases) since both these conditions share similar risk factors. In addition, each of these conditions strongly predisposes to the other [32]. Women and men with AF have an eleven-fold and three-fold higher risk, respectively, of developing heart failure. The combined presence of these two conditions doubles the risk of death [33-35]. Mortality in patients with AF is high and has not changed significantly over time. In the USA in the period 1993-2007, among subjects aged 65 years or older, it is about 10% at 30 days from the first episode of AF, 25% at 1 year and 42% at three years [14a]; in Sweden, among all the patients with AF, total mortality is 40% at 5 years and 60% at 10 years respectively versus 20% and 40% in those without AF [36]. Sub-

jects with persistent and permanent AF are those with a greater probability of dying [37,38] although a direct relationship between arrhythmia and death has not yet been shown. On this regard, however, the results of a recent observational large study performed in Canada seem to support the importance of AF as an independent risk factor of increased mortality. In this study it appears that pursuing the "*rhythm control*" strategy (see next chapter) reduces significantly the risk of death in the long-term period [39].

Treatment strategies and therapy of AF

The Guidelines on the management of AF suggest a therapeutic approach based substantially on two sequential steps: 1) prevention of thromboembolic events when indicated and 2) antiarrhythmic treatment based on two different strategies: "*rhythm control*" and "*rate control*". In particular, Guidelines suggest that the prevention of thromboembolic events should be pursued with OAC when patients present a value of CHADS$_2$/CHA$_2$DS$_2$-VASc risk score ≥ 2, with OAC or antiplatelet agents when the score is 1 and without any antithrombotic agent when the score is < 1. Antiarrhythmic treatment may be implemented by using a "*rhythm control strategy* " which aims to restore and maintain sinus rhythm as much as possible (suggested in the presence of significant symptoms, in younger people and in those refractory to antiarrhythmic therapy) or a "*rate control strategy*" which aims to maintain a physiological level of ventricular frequency, leaving the atria free to fibrillate or not [1]. In the real world, these recommendations are not always followed carefully. The most frequent deviations from the suggestions of the Guidelines regard the appropriate use of OAC followed by the inadequate assignment to antiarrhythmic strategy or specific antiarrhythmic drugs [40,41].

Antithrombotic therapy. Two main problems characterize antithrombotic therapy in the clinical setting of AF: the adherence to Guidelines recommendations that cannot yet be considered as optimal and the introduction in the field of anticoagulation of new agents easier and safer to use, the so called NOAC (Novel Oral Anticoagulants) which are going to replace vitamin-K-antagonists. According to the data of the literature, patients with a CHADS$_2$/CHA$_2$DS$_2$-VASc score ≥ 2 (potential candidates for anticoagulation) represent 48%-63% of the entire population with AF. In these patients, warfarin is used only in 46%-53% of cases if they are managed in the community by the GPs and in 55%-65% if treated in hospital by cardiologists or in

mixed clinical settings (in-hospital/community) by cardiologists and GPs in collaboration or by out-of-hospital cardiologists [4,8,10,12,13,42-45]. Although in the last two decades warfarin use has grown significantly (in Italy from 32% in 2009 to 46% in 2012; in England from 30% in 1994 to 60% in 2003; in the USA from 30% in 1992 to 65% in 2007), in the real world slightly less than half of patients with a clear indication to anticoagulation still does not receive OACs[28,46,47]. In particular, in this half of patients only 50% does not receive OACs because of a real contraindication (high hemorrhagic risk, patient's refusal, logistic difficulties, inadequate control of INR values, difficulties in maintaining adequate INR values, etc) while in the remaining 50% the choice of not using OACs is not justified by any valid reason [2,4,48]. This means that in the real world approximately one-fifth/one fourth of all AF patients at high risk of thromboembolic events is left to his fate [2,4,48]. The reasons for this scenario seem to lie in the results of some studies showing that the incorrect prescription of OACs in patients with AF is largely due to the erroneous beliefs of physicians (for example: non-necessity of OAC therapy in particular clinical conditions where the benefit is proven, excessive fear of bleeding, low familiarity with the use of OACs) [40,41]. This is particularly true when considering the results of some recent observational studies that show that the use of OAC is much more frequent among cardiologists than internists or GPs, and among patients managed in hospital in comparison with those managed in the community [4,12,49,50]. In the complex process of AF management this is a significant weakness that requires further efforts to implement Guidelines recommendations. In this setting, the availability of NOACs (dabigatran, apixaban, rivaroxaban) which show equal efficacy and a safer profile in comparison with warfarin would contribute to improve the quality of care and increase the attitude of the physician to use OACs [51-56].

Antiarrhythmic therapy. As for anticoagulation also for the antiarrhythmic treatment the management of AF patients varies considerably depending on the clinical setting where the patients are treated and the characteristics of the attending physicians [42,56,57]. In the community, the most frequent followed strategy is *"rate control"* pursued in 55%-70% of cases. More in detail, the use of *"rate control"* and *"rhythm control"* varies in relation to the specialty of the attending physician. Among cardiologists, the most frequent pursued strategy is *"rhythm control"* either in hospital wards (ATA-AF study: cardiologists 40% vs internists 13%) or in outpatient clinics (AFFECTS Study: 64% of pa-

tients). On the contrary, *"rate control"* is the most preferred strategy among internists (ATA-AF study, in-hospital wards: internists 60% vs cardiologists 43%) [4,10,13,42,56,57]. Clinical variables that contribute most to *"rhythm control"* strategy assignment are the following: characteristics of the attending physician (cardiologist vs. internists), patient discharge from hospital wards and younger age. Contrary to Guidelines recommendations, AF symptoms rarely represent the condition that leads to the choice of *"rhythm control"* strategy assignment [8,42,57].

When considering specific antiarrhythmic therapy, the findings resulting from the real world clinical practice show some important inadequacies in the use of drugs. Also in this setting as well as for anticoagulation therapy, the reasons for this medical behavior are similar: characteristics of the attending physicians (cardiologist vs internist), erroneous beliefs among physicians on the opportunity of pursuing a specific strategy, attitude of the attending physician to the use of different drugs. Attempts to restore sinus rhythm are mostly pursued by cardiologists, and pharmacological cardioversion is the most frequent procedure used by both cardiologists and internists [8,9,44,56,57]. In patients assigned to the *"rhythm control"* strategy the drugs used most are: beta-blockers (28%-75%), followed by amiodarone (9%-18%), class 1c antiarrhythmic agents (5%-45%) and non-dihydropyridine calcium antagonists (5%-26%). Pacemakers, as an additional therapy to pharmacological therapy, are used in 4%-10% of cases, and transcatheter ablation of the arrhythmic substrate in 3%-6%. The most frequent drugs used in patients assigned to *"rate control"* are: beta-blockers (37%-75%) followed by digitalis (24%-29%) and non-dihydropyridine calcium antagonists (9%-27%) [4,10,13,42,57]. In particular, amiodarone is more frequently prescribed in Italy than in Germany and the USA, while beta-blockers are mainly used in the USA. Transcatheter ablation is performed more frequently in Germany than in Italy [8,13,57] (Tab. 2). When considering the use of single antiarrhythmic drugs it appears that the Italian and German physicians show a greater tendency to use amiodarone while verapamil/diltiazem and Class 1c drugs are more often used in the USA. The large use of amiodarone in some countries of Europe seems in disagreement with the suggestions of the ESC Guidelines which recommend its use as a second or third choice; the large use of class Ic antiarrhythmic drugs observed in the USA, although not in disagreement with Guidelines recommendations, should be considered critically due to potential proarrhythmic effects of these agents as

Tabla 2. Therapy of atrial fibrillation

Study	ISAF [4]		AFFECTS [13]		ATRIUM [10]
Therapy	Rhythm	Frequency	Rhythm	Frequency	Total population
Beta-blockers	28.3%	37%	46.5%	51.4%	75%
Class 1c	11%	-	41.5%	16%	5%
Amiodarone/dronedarone	18.7%	-	9.2%	4.8%	11%
Digitalis	-	24%	23%	28.7%	29%
Verapamil/diltiazem	5.2%	9%	26.6%	27.6%	15%
Pacemaker + antiarrhythmic drugs	4.3%	1.7%	-	-	
		(ablate&pace)			10%
Atrial fibrillation ablation	3%				6%

Rhythm: *"rhythm control"* strategy; Rate: *"Rate control"* strategy

reported in a recent survey of the European Heart Rhythm Association [1,58].

Resource consumption to manage AF patients

AF is a long-lasting disease (in about one-half of cases its presence exceeds 5 years) associated often with complicated clinical outcomes and often burdened by disabling symptoms. This confirms and supports our previous considerations on the necessity of an important commitment of human and economic resources to manage its multiple clinical manifestations and consequences. Unfortunately, the calculation of the costs of AF management is a difficult task because detailed data on the amount of clinical contacts, diagnostic tests and therapeutic procedures used to manage patients are scarce and generally related to short spans of time. To assess the real amount of resources used over the time, 4 large surveys have been performed in Europe [4,9,10,59]. In Italy, in the five years preceding the screening of the ISAF study, about 40% of patients assigned to *"rhythm control"* strategy and 47% of those assigned to *"rate control"* were hospitalized for reasons related to AF. Of these patients, approximately one-half was hospitalized at least once, and 10% more than 3 times. Similar frequencies have been found in Germany (up to 3 hospitalizations in 37% of cases, more than 3 in 7%). In addition, both in Italy and Germany in the year preceding the screening 46%-56% of AF patients receive at least one cardioversion to restore sinus rhythm (electrical or pharmacological) and 10% more than 3 attempts [9,10,59]. In Italy, in the 5 years preceding the ISAF screening: 1) a 24h Holter ECG is performed

at least 1 time in half of AF patients and more than 3 times in 11%, 2) an exercise stress test at least one time in one-fourth and more than 3 times in 4%, 3) an echocardiogram at least one time in three-fourths and more than 3 times in 18%, and 4) approximately 4% of patients undergo an electrophysiological invasive test [59]. In Italy and in Germany respectively 3% and 6% of patients are submitted to a transcatheter ablation of the arrhythmogenic substrate, while a further 6% and 10% receive or have received a pacemaker or a defibrillator [4,10]. Unfortunately these surveys do not provide information on the resources used to manage the neurological and social consequences of AF. The only consideration that can be drawn from these findings is that probably the noninvasive evaluation of these clinically complex patients is still quite weak.

A recent review of the annual estimated costs of AF management per patient has shown significant differences between the USA and the Western Europe. Direct costs per patients/per year range from $ 10.100 to 14.200 in the USA and from € 450 to 3000 in the Western Europe with expenditures varying significantly from a minimum of € 1.507 in Greece to a maximum of € 3.225 in Italy. The inclusion of indirect costs increases the total expenditures by 20%. The analysis of costs for a National Health Service has been assessed in the United Kingdom in 2004; from this study it appears that the total annual expenditures for the care of AF patients was approximately € 655 million, the equivalent of 0.97% of the National Health expenditure. The costs increase significantly with aging and the number of recurrences, among females, and among patients assigned to *"rhythm control"* strategy or suffering from multiple comorbidities. Hospitaliza-

tions are the dominant cost driver representing the 44-87% of total expenditure [60,61].

Conclusions

The present analysis allows to conclude the following: 1) worldwide, the prevalence of AF is increasing over time and, very likely, in the general population of the western countries it will achieve a rate of 2.5%-2.6% over the next 15 years; thus, for the National Health Systems it is necessary to plan early the most appropriate interventions to allocate adequately the human and the economic resources, 2) the management of AF still presents weaknesses as far as the diagnostic approach (more careful detection of the patients with AF, poor non-invasive assessment) and the therapeutic approach (underuse of OAC, inadequate choice of the most appropriate antiarrhythmic strategy, inadequate use of antiarrhythmic drugs), 3) a greater investment in educational programs to improve standards of care for AF is desirable.

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