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CONTEMPORARY VIEW OF ATRIAL FIBRILLATION; BEYOND THE EUROPEAN GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION.

TESIS DOCTORAL

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CERTIFICA: que el trabajo titulado: "CONTEMPORAY VIEW OF ATRIAL FIBRILLATION; BEYOND THE EUROPEAN GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION." ha sido realizado bajo su dirección en el Departamento de Cardiología por Moisés Rodríguez-Mañero, Licenciado en Medicina y Cirugía.

Considero que el presente trabajo se encuentra terminado y reúne los requisitos necesarios para que el interesado pueda optar al título de Doctor por la Universidad de Santiago de Compostela.

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“Para aprender a enseñar hay que aprender a aprender” (A. Einstein)

A mi familia
A mis amigos
A mis maestros
A mis pacientes

INDEX

INTRODUCTION

INTRODUCTION

Atrial fibrillation (AF) affects up to 5 million people in the United States, and data suggest that as the population ages, the incidence will continue to increase[1,2]. The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year[3]. The rate of death among patients with AF is about double that among patients with normal sinus rhythm[3]. The overall cost of treating recurrent AF has been estimated to be more than 6.5 billion (dollars) per year[4]. Importantly, as we will discuss later, it seems, that not only prevalence of AF is progressively increasing but also the risk profile of patients with AF.

AF is usually a progressive disease. The natural history often begins with infrequent episodes of limited duration termed paroxysmal AF (often defined as episodes that terminate spontaneously within 1 week). Such episodes then tend to become more frequent and longer in duration, progressing to persistent AF (which fails to terminate spontaneously within 7 days and may require cardioversion) or permanent AF (if the arrhythmia lasts for more than 1 year and cardioversion either has not been attempted or has failed). Symptoms include palpitations, shortness of breath, and fatigue; particularly for symptomatic patients, AF has adverse effects on quality of life[3]. Outstandingly, AF confers a 5-fold risk of stroke, and one in five of all strokes are attributed to this arrhythmia. In this regard, the identification of various stroke clinical risk factors has led to the publication of various stroke risk schemes[3]. Most have (artificially) categorized stroke risk into ‘high’, ‘moderate’, and ‘low’ risk strata. The simplest risk assessment scheme is the CHADS2 score. The CHADS2 [cardiac failure,

hypertension, age, diabetes, stroke (doubled)] risk index evolved from the AF Investigators and Stroke Prevention in AF (SPAF) Investigators criteria, and is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age ≥ 75 years, a history of hypertension, diabetes, or recent cardiac failure.

Thus, the CHADS2 stroke risk stratification scheme should be used as an initial, rapid, and easy-to-remember means of assessing stroke risk. In patients with a CHADS2 score ≥2, chronic OAC therapy with a VKA is recommended in a dose-adjusted approach to achieve an international normalized ratio (INR) target of 2.5.

Recently, in the last guidelines for the management of AF other 'clinically relevant non-major' risk factors (previously referred to as 'less validated risk factors') include female sex, age 65 – 74 years, and vascular disease (specifically, myocardial infarction, complex aortic plaque and periferical artery disease (PAD)). Note that risk factors are cumulative, and the simultaneous presence of two or more 'clinically relevant non-major' risk factors would justify a stroke risk that is high enough to require anticoagulation. This risk factor-based approach for patients with non-valvular AF can also be expressed as an acronym, CHA2DS2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 – 74, and sex category (female)]. This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or

angiographic evidence of PAD, etc.), and female sex. Thus, this acronym (CHA2DS2-VASc) extends the CHADS2 scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate. The true magnitude of these recommendations has not yet been quantified and will be also analysed in detail along this pages.

The electrophysiological basis of AF requires both a trigger that initiates the dysrhythmia and a substrate that can sustain it[5,6]. Althougt AF can be precipitated by several causes as we will discuss later on (channelopathiesas, slow auriculoventricular nodal tachycardia, etc), the most common triggers of AF are ectopic atrial beats that arise from the muscle sleeves of the pulmonary veins[7,8]. These triggers may be provoked by the intrinsic activity of cardiac ganglionic plexuses, which are clustered in the vicinity of the pulmonary vein–left atrial junction[9,10]. The pulmonary vein–left atrial junction and an enlarged atrium harboring fibrosis and inflammation serve as the substrate for sustaining wavelets of AF. With persistence of AF, a further electrophysiological change in the atria - namely, shortening of the refractory period of the atrial muscle - occurs and predisposes to the development of other triggers and wavelets. This process results in perpetuation of AF and in a greater predisposition to AF. Maintenance of sinus rhythm can reverse these changes and mechanisms. Hence, AF begets atrial fibrillation, and sinus rhythm begets sinus rhythm[11-13]. Whether to restore and maintain sinus rhythm ("rhythm control") or allow AF to continue while controlling ventricular rate ("rate control") remains a key decision steeped in controversy. Given the poor outcomes associated with AF[3], rhythm control makes intuitive sense. However, it remains unclear whether AF causes

death or is simply a marker of risk. Despite the association of AF with excess morbidity and mortality, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial and multiple other studies failed to demonstrate reduction in death, stroke, or hospitalization with rhythm control compared with rate control, assuming appropriate anticoagulation as part of either strategy[14-18]. Even in patients with systolic dysfunction and clinical heart failure, in whom AF is a predictor of death and frequent cause of decompensation, the Atrial Fibrillation and Congestive Heart Failure trial identified no difference in overall survival, cardiovascular death, worsened heart failure, or stroke at 37 months with rhythm control[19].

The apparent discrepancy between the poor outcomes associated with AF in epidemiologic studies and the failure of multiple trials to demonstrate a substantial benefit from a rhythm-control strategy reflect the limited efficacy and adverse effects of the available antiarrhythmic medications used in these studies to maintain sinus rhythm. The proportion of patients actually achieving sinus rhythm with antiarrhythmic drugs in randomized trials, ranging from 26% to 63%[14-18], illustrates this limited efficacy. Nearly all antiarrhythmic medications carry a risk of ventricular proarrhythmic toxicity. In addition, the predominant antiarrhythmic drug in these studies, amiodarone (used in 62.8% of patients in the rhythm control arm of AFFIRM[14] and in 82% of patients in Atrial Fibrillation and Congestive Heart Failure[19]), has substantial extracardiac toxicity, including pulmonary and hepatic toxicity, thyroid dysfunction, and bradycardia. Furthermore, because the “rate versus rhythm control” trials generally involved older patients with comorbidities, the results cannot be extrapolated to younger, healthier patients who would face the consequences of AF for longer periods

with a rate-control strategy. The results of these studies should therefore not be interpreted as a lack of benefit of restoring sinus rhythm, but rather that the toxicity and limited efficacy of available antiarrhythmic medications make their routine use no better than rate control to achieve freedom from stroke and death. In support of this concept, a post hoc analysis of AFFIRM demonstrated that sinus rhythm was associated with a lower risk of death independently of the medications used compared with the presence of AF, and after adjustment for the rhythm, antiarrhythmic medications increased mortality[20].

Antiarrhythmic drugs are considered the first-line treatment for maintenance of sinus rhythm. However, the efficacy of these agents is not favorable, with only 50% of patients so treated maintaining sinus rhythm after 1 year of follow-up[21,22]. In addition, as we pointed out previously, the side effects of antiarrhythmic drugs are not trivial. In a recent meta-analysis, these side effects included treatment-related death in 0.5% of patients, torsades de pointes in 0.7%, neuropathy in 5.0%, and thyroid dysfunction in 3.3%[23]. Less serious side effects such as gastrointestinal symptoms occur more frequently and may have a substantial effect on quality of life.

In regard with the medical treatment is important to highlight that in some situations AF coexist with common atrial flutter (AFl). As a matter of fact it is a well-recognized and commonly encountered occurrence in the clinical setting[3]. It has been shown that antiarrhythmic drugs can organize AF into AFl[14]. The administration of AAD to patients with AF allows for the formation of these lines of functional block and hence organization into AFl. Hybrid therapy is a management strategy that consists of the ablation of cavotricuspid isthmus

(CTI) and continued pharmacologic therapy when treatment with Class I or III AAD organizes AF into AFl. Numerous studies have shown hybrid therapy to be an effective treatment with AF recurrences rates ranging between 11 and 27%[3]. However, these studies have been limited by short follow-up periods. In the present thesis, we aimed to focus also on the AF recurrence, stroke and death during long-term follow-up in a cohort of patients with AF to AFI conversion following treatment with antiarrhythmic drugs - AFl compared with patients with coexisting AF and AFl after radiofrequency catheter ablation of CTI.

Catheter ablation is indicated to prevent the recurrence of symptomatic AF in patients in whom medical therapy has been ineffective. AF ablation is a therapeutic technique that uses radiofrequency energy or freezing to destroy atrial tissue that is involved in the propagation of the dysrhythmia. Radiofrequency ablation generates an alternating electrical current that passes through myocardial tissue, creating heat energy that conducts to deeper tissue layers. At temperatures of 50°C or higher, most tissues undergo irreversible coagulation necrosis and then evolve into nonconducting myocardial scar tissue[24,25]. Cryoablation destroys tissue by freezing.

The principal objective of AF ablation is the electrical disconnection of the pulmonary-vein triggers from the atrial substrate (often called “pulmonary-vein isolation”)[26,27]. To achieve this goal, ablation is performed around the pulmonary-vein orifice. Ablation of sites beyond the pulmonary vein–left atrial junction in the atrial substrate itself, targeting so-called complex fractionated electrograms, is not necessary in paroxysmal AF but may be very important in patients with persistent AF[27].

Several randomized trials have shown superior outcomes for radiofrequency ablation as compared with antiarrhythmic drug therapy[28-35]. For example, in one trial, 198 patients with paroxysmal AF in whom antiarrhythmic drug therapy had previously failed were randomly assigned to either radiofrequency ablation or antiarrhythmic drug therapy with other agents[32]. Patients assigned to catheter ablation received antiarrhythmic drug therapy for the first 6 weeks after treatment, and recurrences during this interval were not included in the primary trial end point (a so-called blanking period to allow healing of the atrial myocardium after the procedure). At 1 year, 86% of the patients assigned to catheter ablation and 22% of those assigned to antiarrhythmic drug therapy had not had a recurrent atrial tachyarrhythmia ($P<0.001$). Hospitalizations for cardiovascular disease were also less frequent in the ablation group.

In another trial, 167 patients with drug-resistant paroxysmal AF were randomly assigned to ablation or another antiarrhythmic drug[33]. At 9 months, 63% of the patients assigned to catheter ablation and 17% of those assigned to antiarrhythmic drug therapy were free of recurrent atrial tachyarrhythmias. Patients in the ablation group also had significantly greater improvement in quality of life.

Cryoablation has also been shown to be effective. In the STOP AF trial, 245 patients with paroxysmal AF in whom previous antiarrhythmic drug therapy had failed were randomly assigned to treatment with a cryoablation balloon or antiarrhythmic drugs. One year after treatment, 69.9% of the patients treated with cryoablation had no detectable AF, as compared with 7.3% of those who were treated with antiarrhythmic medications[34]. Minimally thoracoscopic

ablation has also been performed in the last years in order to achive pulmonary vein isolation, and although results seem to be superior to those obtained endocardially, it is subject to potential complications.

A recently published survey reported data on 16,309 patients undergoing AF ablation worldwide, including data on adverse events. Almost all the procedures in this survey were performed with the use of radiofrequency ablation; cryoablation was used in less than 2% of cases. In this survey, the risk of a major complication was 4.5%[35]. The risk of death was 0.15%.

Cardiac tamponade due to perforation is a potentially life-threatening complication occurring in approximately 1.3% of patients undergoing AF ablation. Cardiac perforation can be secondary to a misdirected transseptal puncture, trauma due to catheter movement, or excessive focal application of radiofrequency energy. Direct injury to the phrenic nerve can also occur as a result of ablation near the right superior pulmonary vein and superior vena cava. Such injury can cause diaphragmatic paralysis. Esophageal injury has been reported in approximately 10% of patients; atrioesophageal fistulas are rare (occurring in 0.04% of patients) but can be devastating and even lethal[33].

Cerebrovascular thromboembolism has been reported to occur in up to 2% of patients[33]. Thromboembolic complications can arise because of clot or char formation on the sheaths and catheters or at the site of ablation. The diagnosis is usually made during the procedure, but thromboemboli can occur several days later.

Pulmonary-vein stenosis is a late complication of ablation caused by injury to the pulmonary vein musculature. The reported incidence varies from 0 to 10%.

Symptoms of pulmonary-vein stenosis include chest pain, shortness of breath, cough, and recurrent lung infections[33]. The diagnosis is made with the use of computed tomographic imaging or magnetic resonance scanning or by means of ventilation–perfusion lung scanning.

Iatrogenic atypical flutter, a type of regular atrial arrhythmia encountered after ablation, can result from ablation lines that do not completely isolate the pulmonary veins. The occurrence of this complication depends to a large extent on the technique of ablation; the incidence ranges from 1.8 to 14.3%. Nevertheless, pulmonary vein stenosis has never been described in the setting of thoracoscopic approach, were however there is a potential risk of conversion to sternotomy, pleural effusion and pneumothorax.

Finally, as abovementioned, although several advances in the field of AF ablation have been done in the recent years, fewer progresses have been made in the field of AFI ablation procedures. As it well known, the reentrant circuit through the CTI is located in the right atrium and the left atrium is then activated passively. Therefore, radiofrequency ablation of AFI appears as a reasonable approach regarding feasibility, effectiveness, and it is considered as a low procedural risk[3]. Most studies on ablation-related complications concern all indications of ablation, however, little is known about the risk of pacemaker (PCM) implantation after uneventful successful CTI ablation in the long term follow up, aspect that will be discuss at the end of the present thesis.

HYPOTESIS

HYPOTESIS

- Based on epidemiological studies, AF prevalence has increased significantly over the last decade. We hypothesize that a radical change in the risk profile for thromboembolic events in patients with AF has additionally ensued, as also a change in the use of oral anticoagulants and upstream therapies.

- The most widely used system for the tromboembolic prevention is the CHADS2 scale. Due to the limitations of this scale, the current guidelines (European Society of Cardiology) emphasize other ‘‘modulating’’ factors that were previously not taken into consideration, such as vascular disease or female sex, and it proposes a new classification system, the so called ‘‘CHA2DS2-VASc’’ scale. It is our hypothesis that this new approach wills reclassifies a substantial number of patients previously considered ‘‘low’’ or ‘‘moderate’’ risk into higher categories, with the subsequent increase of the indication for OAC.

- Some percentage of patients with AF can have “lone AF,” which can be, in certain cases, of hereditary origin. Accordingly, during previous years, numerous inherited cardiac syndromes associated with AF have been identified, including Brugada syndrome (BS). Moreover, AF can even be the first manifestation of latent BS. We postulate that a relevant percetage of patients with BS have AF as first clinical manifestation.

- At the present time no prospective studies have been conducted in patients with AF but absence of heart failure. We assume that rate of admissions due to any cause or due to cardiovascular cause in this subgroup of patients are higher than in patients without left bundle branch block.

- Evidence supporting the use of digoxine is nowadays a matter of controversy, mainly as a rate control in patients with AF. We hypothesize that digoxine could be a useful drug in a subgroup of patients, without deleterous effect (in terms of cardiovascular mortality and hospital admissions).

- We postulate that the so-called "*hybrid therapy*" (management strategy that consists of the ablation of CTI and continued pharmacologic therapy with Class I or III AAD), presently established in the ESC guidelines, is not an effective therapy for long-term control of AF.

- Finally, we hypothesize that in patients with history of CTI ablation for common AFL, ECG Intraventricular conduction disturbance and slow ventricular response at the time of the ablation might be strong predictors of the need of PMI in the long term.

OBJECTIVES

OBJECTIVES

- To define trends in AF prevalence and its medical management using recent data based on data from two cross-sectional studies performed in a European country in 1999 and 2009.

- To analyze the impact of classifying patients with AF according to the CHA2DS2-VASc scale in comparison to the CHADS2 scale, and to test the new oral anticoagulant recommendations in a sample of patients with AF recruited from primary care and cardiology outpatient clinics.

- To assess the prevalence of AF as first clinical manifestation in patients with Brugada Syndrome, their demographic, clinical characteristics and diagnosis management in a large cohort of patients collected in a reference hospital in the field of the Brugada Syndrome.

- To determine whether left bundle-branch block associated with AF has an independent, cumulative effect on mortality for patients without congestive heart failure.

- To assess and compare the effect of digoxin on clinical outcomes in patients with AF versus those under beta-blokers or none, in patients with and without heart failure.

- To determine the long-term effectiveness of hybrid therapy in the control of AF as well as the differences in clinical outcomes between patients with antiarrhythmic drug AFI, those with coexistent AFI and AF, and isolated AFI.

- To assess the outcomes in terms of pacemaker implantation and potential predictors after uneventful successful radiofrequency ablation procedure of typical AFI.

RESULTS

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SPECIAL ARTICLE

Trends in clinical profile and medical treatments of atrial fibrillation patients over the last 10 years

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KEYWORDS
Atrial fibrillation;
Risk factors;
Oral anticoagulation;
Upstream therapies

Abstract
Aim: We sought to define trends in AF prevalence and its medical management using recent data based on data from two cross-sectional studies performed in a European country in 1999 and 2009.
Methods: CARDIOTENS 1999 and CARDIOTENS 2009 were two observational, cross-sectional, multicenter studies. Patients were recruited in from primary care and cardiology outpatient clinics. A total of 32 051 and 25 137 subjects were analyzed in the two studies, 1540 and 1524 of them, respectively, diagnosed with AF.
Results: Over the course of the study period there was an increase in the prevalence of AF (from 4.8% to 6.1%), mainly due to the higher prevalence of AF in patients aged over 70 years (24.7% vs. 37.1%). Furthermore, patients with AF had a higher prevalence of hypertension (64.9% vs. 87.0%), diabetes (19.0% vs. 37.4%), heart failure (30.8% vs. 34.8%), coronary artery disease (23.0% vs. 25.8%) and previous stroke (1.5% vs. 8.9%). An overall increase in prescription of antithrombotic/antiplatelet therapy was observed (33.0% vs. 62.7% and 31.0% vs. 38.2% respectively); the difference observed in 1999 between prescription of oral anticoagulation by general practitioners and cardiologists was not seen in the later study. Differences in prescription of angiotensin-converting enzyme inhibitors (28.0% vs. 40.7%), angiotensin receptor blockers (10.0% vs. 40.0%), beta-blockers (14.0% vs. 41.5%) and calcium channel blockers (21.0% vs. 34.9%) were also identified.

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Conclusions: The number of patients with AF and a higher risk for thromboembolic events increased over the last 10 years. More aggressive antithrombotic treatment has been observed, especially in older patients.

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Original article

Impact of New Criteria for Anticoagulant Treatment in Atrial Fibrillation

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A B S T R A C T

Introduction and objectives: The guidelines for the management of atrial fibrillation (AF) incorporate new risk factors for thromboembolism, trying to de-emphasize the use of the 'low', 'moderate', and 'high' risk categories. The objective of this study was to determine the impact of the new scheme CHA_2DS_2-VASc and of the new recommendations for oral anticoagulation (OAC) in a contemporary sample of patients with AF seen by primary physicians and cardiologists.
Methods: Multicenter, observational, cross-sectional study on the epidemiology of hypertension and its control, designed by the arterial hypertension department. Each researcher enrolled the first 6 consenting patients who came for examination during a 5-day period.
Results: Of 25 137 individuals recruited, 1544 were diagnosed with AF. The vast majority of the sample had a $CHADS_2$ score $\geq$2 (77.3%). Individuals with a risk score lower than 2 were categorized according to the CHA_2DS_2-VASc score: 14.4% were aged 75 years or older (CHA_2DS_2-VASc = 2). Of those younger than 75, 42.3% had a CHA_2DS_2-VASc = 2; 23.7% CHA_2DS_2-VASc = 3, and 1.1% CHA_2DS_2-VASc = 4. This means that the 85.1% of the patients with a $CHADS_2$ score $<$ 2 and no contraindications are indicated for OAC.
Conclusions: The new recommendations will result in a significant increase in patients with indications for OAC, at the expense of those previously characterized as low-to-moderate risk. Therefore, patients at risk of thromboembolic events must be identified, although an evaluation of bleeding risk should be part of the patient assessment before starting anticoagulation.

Impacto de los nuevos criterios para el tratamiento anticoagulante de la fibrilación auricular

Palabras clave:
Fibrilación auricular
Escalas de riesgo
Fármacos antitrombóticos

R E S U M E N

Introducción y objetivos: Las guías de fibrilación auricular (FA) de la Sociedad Europea de Cardiología incluyen en la estratificación del riesgo tromboembólico nuevos factores «moduladores» que recalifican a un porcentaje de pacientes anteriormente catalogados de riesgo «bajo» o «moderado» a categorías superiores. El objetivo de nuestro estudio es analizar el impacto de la escala CHA_2DS_2-VASc y las nuevas recomendaciones de anticoagulación oral (ACO) en una muestra contemporánea de pacientes con FA reclutados en consultas externas de cardiología y atención primaria.
Métodos: Estudio epidemiológico observacional, transversal y multicéntrico diseñado por la sección de hipertensión arterial con el objetivo de conocer la prevalencia y el control de la hipertensión en la práctica clínica habitual. Cada médico debía incluir a los primeros 6 pacientes de cada día durante 5 días.
Resultados: Se reclutó a 25.137 pacientes, de los que 1.544 tenían el antecedente de FA. De estos, el 77,3% tenía una puntuación $CHADS_2 \geq 2$. Se recalificó según la escala CHA_2DS_2-VASc a la población restante con $CHADS_2 < 2$. El 14,4% tenía $\geq$ 75 años (CHA_2DS_2-VASc = 2). De los menores de 75 años, el 42,3% tenía un CHA_2DS_2-VASc = 2; el 23,7%, CHA_2DS_2-VASc = 3 y el 1,1%, CHA_2DS_2-VASc = 4. Esto supone que el 85,1% de los pacientes con $CHADS_2 < 2$ tendrán, en ausencia de contraindicaciones, indicación de ACO.
Conclusiones: Las nuevas indicaciones supondrán un incremento significativo en el número de pacientes con indicación de ACO, a expensas de los previamente categorizados como con riesgo «bajo-moderado».

SEE RELATED ARTICLE:
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Prevalence, Clinical Characteristics and Management of Atrial Fibrillation in Patients With Brugada Syndrome

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Atrial fibrillation (AF) can be the first manifestation of latent Brugada syndrome (BS). The aim of our study was to assess the prevalence of AF as the first clinical diagnosis in patients with BS and their demographic and clinical characteristics and diagnosis management in a large cohort of patients. The patient group consisted of 611 patients with BS. The data from those with a diagnosis of AF previous to the identification of BS were analyzed (n = 35). Eleven cases were unmasked after the initiation of a class I antiarrhythmic drug and one during the establishment of general anesthesia. In the remaining population, BS was diagnosed using an ajmaline test performed mainly because of younger age in patients with lone AF (n = 13), previous syncope or sudden cardiac death (n = 3), or a clinical history of sudden cardiac death in the family (n = 5). The mean patient age was 49 ± 15 years, 21 were male patients, 14 had a family history of sudden death, 15 had had previous syncope, and 4 had survived cardiac arrest. Concomitant electrical disorder was found in 13 patients. Remarkably, 21 patients had normal findings on the baseline electrocardiogram. In conclusion, AF could be one of the first clinical manifestations of latent BS in a considerable number of patients. This identification is crucial because the treatment of these patients is subject to relevant changes. The ajmaline test plays an essential role, mainly in young patients with a family history of sudden death, despite having normal findings on a baseline electrocardiogram. **(Am J Cardiol 2013;111:362−367)**

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Imagen en cardiología

Doble respuesta nodal incesante y fibrilación auricular paroxística

Incessant Double Ventricular Response and Paroxysmal Atrial Fibrillation

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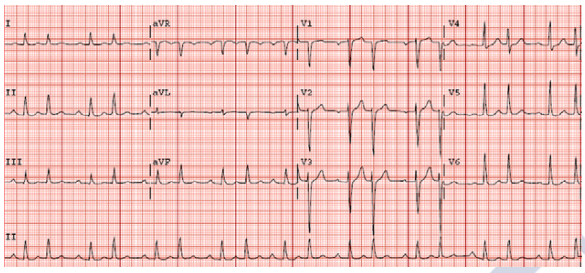

Figura 1.

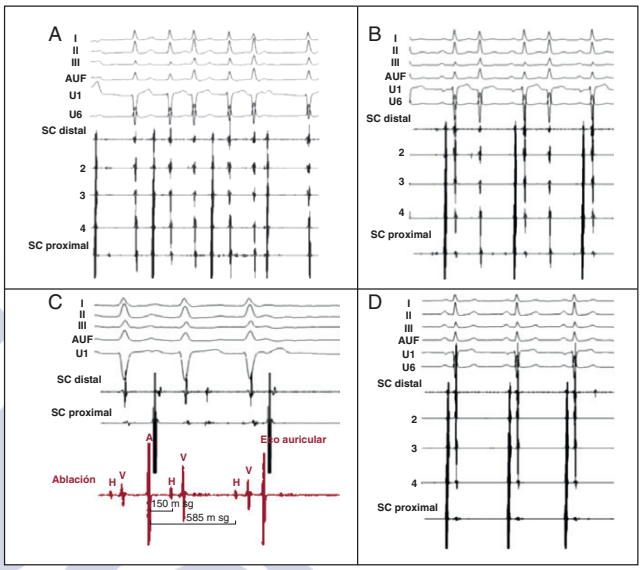

Figura 2.

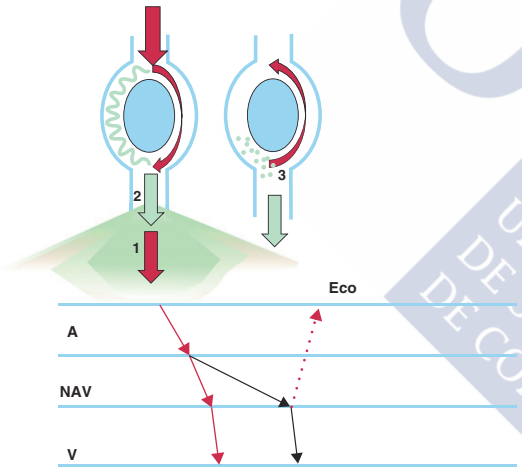

Figura 3.

La fibrilación auricular puede desencadenarse por ritmos auriculares rápidos, entre ellos la taquicardia intranodal. Se presentan los

http://www.ncbi.nlm.nih.gov/pubmed/21497976

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Left bundle branch block in atrial fibrillation patients without heart failure

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Grupo Barbanza investigators, Germán Allut-Vidal, Jorge Alvear-García, Carmen Besada-Gesto, Ricardo Besada-Gesto, Rubén Blanco-Rodríguez, David Bouza-Álvarez, Carmen Caneda-Villar, Concepción De Frutos-De Marcos, Ma Jesús Eirís-Cambre, Mario Fandiño-Pazos, Juana Fernández-Moreno, José Ma Fernández-Villaverde, José L. Gómez-Vázquez, Ángel Herrero-Suárez, Ángel Lado-Llerena, Manuel Lado López, Ramón Lafuente-Taboada, Rosa Liñares-Stolle, Javier Maestro-Saavedra, Virtudes Muiño-Vázquez, Augusto Nores-Lorenzo, Manuel Otero-Mata, Fernando Otero-Raviña, Miguel Pérez-Llamas, José M. Rodríguez-García, Esperanza Rodríguez-Moldes, Victorino Turrado-Turrado, Leopoldo Vaamonde-Mosquera, José A. Vázquez-Mallo, Javier Ventosa-Rial, Juan Vidal-Sampedro, Andrés Vizcaya-Ramos, Lucrecia Zugaza-Gurruchaga

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Original article

Outcomes of a Contemporary Sample of Patients With Atrial Fibrillation Taking Digoxin: Results From the AFBAR Study

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ABSTRACT

Introduction and objectives: We aimed to assess and compare the effect of digoxin on clinical outcomes in patients with atrial fibrillation vs those under beta-blockers or none of these drugs.
Methods: AFBAR is a prospective registry study carried out by a team of primary care physicians (n = 777 patients). Primary endpoints were survival, survival free of admission due to any cause, and survival free of admission due to cardiovascular causes. The mean follow up was 2.9 years. Four groups were analyzed: patients receiving digoxin, beta-blockers, or digoxin plus beta-blockers, and patients receiving none of these drugs.
Results: Overall, 212 patients (27.28%) received digoxin as the only heart control strategy, 184 received beta-blockers (23.68%), 58 (7.46%) were administered both, and 323 (41.57%) received none of these drugs. Digoxin was not associated with all-cause mortality (estimated hazard ratio = 1.42; 95% confidence interval, 0.77-2.60; *P* = .2), admission due to any cause (estimated hazard ratio = 1.03; 95% confidence interval, 0.710-1.498; *P* = .8), or admission due to cardiovascular causes (estimated hazard ratio = 1.193; 95% confidence interval, 0.725-1.965; *P* = .4). No association was found between digoxin use and all-cause mortality, admission due to any cause, or admission due to cardiovascular causes in patients without heart failure. There was no interaction between digoxin use and sex in all-cause mortality or in survival free of admission due to any cause. However, an association was found between sex and admission due to cardiovascular causes.
Conclusions: Digoxin was not associated with increased all-cause mortality, survival free of admission due to any cause, or admission due to cardiovascular causes, regardless of underlying heart failure.

Seguimiento clínico de una muestra contemporánea de pacientes con fibrilación auricular en tratamiento con digoxina: resultados del estudio AFBAR

Palabras clave:
Fibrilación auricular
Digoxina
Ingreso cardiovascular

RESUMEN

Introducción y objetivos: Evaluar el efecto de la digoxina en los resultados clínicos de los pacientes con fibrilación auricular con y sin tratamiento con bloqueadores beta.
Métodos: El AFBAR es un registro prospectivo llevado a cabo por un equipo de médicos de atención primaria (n = 777 pacientes). Los objetivos principales fueron la supervivencia, la supervivencia libre de hospitalización por cualquier causa y la supervivencia libre de hospitalización por causas cardiovasculares. La media de seguimiento fue 2,9 años. Se analizaron cuatro grupos: pacientes tratados con digoxina, bloqueadores beta o digoxina más bloqueadores beta, y pacientes que no recibían ninguno de estos fármacos.
Resultados: En total, 212 pacientes (27,28%) recibieron digoxina como única estrategia de control de frecuencia; 184 recibieron bloqueadores beta (23,68%); 58 (7,46%), ambos fármacos y 323 (41,57%), ninguno de ellos. El tratamiento con digoxina no se asoció a la mortalidad por todas las causas (razón de riesgos estimada = 1,42; intervalo de confianza del 95%, 0,77-2,60; p = 0,2), la hospitalización por todas las causas (razón de riesgos estimada = 1,03; intervalo de confianza del 95%, 0,710-1,498; p = 0,8) ni la hospitalización por causas cardiovasculares (razón de riesgos estimada = 1,193; intervalo de confianza

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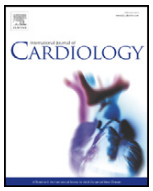

Failure of hybrid therapy for the prevention of long-term recurrence of atrial fibrillation☆,☆☆,★,★★

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ABSTRACT

Objectives: To determine the long-term effectiveness of hybrid therapy in the control of atrial fibrillation (AF) as well as the differences in clinical outcomes between patients with antiarrhythmic drug atrial flutter (AAD-AFl), those with coexistent AFl and AF, and isolated AFl.
Methods: Four hundred eight patients who consecutively underwent cavotricuspid isthmus (CTI) ablation between 1998 and 2010 were followed for 5.9 years. Twenty-seven patients had AAD-AF1 (Group 1): they had AF but not AFl at baseline but on AAD therapy they showed typical AFl. They underwent CTI ablation and continued with AAD therapy, 96 patients had coexistent AF1 and AF at baseline (Group 2) and continued with AAD therapy at the discretion of their cardiologists and 284 patients had isolated AFl (Group 3).
Results: AF recurred in the majority of the AAD-AF1 patients (74%, incident density rate (IDR): 19.1/100 person-years). This incidence rate was similar to the recurrence rate of AF in patients with coexistent AFl and AF (59%, IDR: 19.2/100 person-years). The patients in Group 1 had a similar IDR of stroke as Group 2 and a slightly higher rate than Group 3. There were no significant differences in the IDR for death among Groups 1, 2 and 3.
Conclusions: Hybrid therapy was not effective for long-term control of AF. The clinical outcomes (AF, stroke and death) were similar for AAD-AF1 patients and patients with coexistent AF and AFl.

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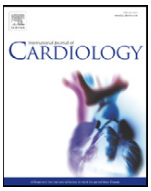

Risk of pacemaker implantation after uneventful successful cavotricuspid isthmus radiofrequency ablation in patients with common atrial flutter

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ABSTRACT

Introduction: Little is known about the risk of pacemaker implantation after common atrial flutter ablation in the long-term.
Methods: We retrospectively reviewed the electrophysiology laboratory database at two Spanish University Hospitals from 1998 to 2012 to identify patients who had undergone successful ablation for cavotricuspid dependent atrial flutter. Cox regression analysis was used to examine the risk of pacemaker implantation.
Results: A total of 298 patients were considered eligible for inclusion. The mean age of the enrolled patients was 65.7 ± 11. During 57.7 ± 42.8 months, 30 patients (10.1%) underwent pacemaker implantation. In the stepwise multivariate models only heart rate at the time of the ablation (OR: 0.96; 95% CI: 0.93–0.98; $p < 0.0001$) and intraventricular conduction disturbances in the baseline ECG (OR: 3.87; 95% CI: 1.54–9.70; $p = 0.004$) were independents predictors of the need of pacemaker implantation. A heart rate of ≤65 bpm was identified as the optimal cut-off value to predict the need of pacemaker implantation in the follow-up (sensitivity: 79%, specificity: 74%) by ROC curve analyses.
Conclusion: This is the first study of an association between the slow conducting common atrial flutter and subsequent risk of pacemaker implantation. In light of these findings, assessing it prior to ablation can be helpful for the risk stratification of sinus node disease or atrioventricular conduction disease requiring a pacemaker implantation in patients with persistent atrial flutter.

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0167-5273/

DISCUSSION

DISCUSSION

Atrial fibrillation is the most common sustained cardiac arrhythmia in clinical practice[1,2]. What was defined in the past as a simple arrhythmia characterized by irregularly irregular heartbeats is now accepted as a common and rapidly growing clinical problem and as a disease entity. As a matter of fact, it has generated a wide range of research in the last years, particularly in the last two decades. Nevertheless, as we have tried to reflect through the course of this thesis, there are still lots of doubts that deserve further investigation. We have stopped in some points.

First of all, based on the CARDIOTENS study, we have focused in the epidemiology, treatment and risk profile of patients with AF at the current moment and the trend in the last decade, showing that not only AF prevalence has increased but also, the current AF population exhibits a higher risk profile for thromboembolic events, leding to radical changes in the use of oral anticoagulants and emphasis on upstream therapies.

Secondly we have tried to define the impact of the new scheme (CHA2DS2-VASc) in a contemporary sample of patients with AF. As we have hypothesized, these new indications will imply a significant increase in the number of patients with indications for this type of therapy, at the expense of those previously categorized as low-to-moderate risk.

Thirdly, based on in-hospital data, we have shown that “lone AF” is not always “lone”, and could be the first manifestation of a latent Brugada Syndrome. Besides Brugada Syndrome, some other circunstanes, as for example, dual AV

node, can simulate or trigger an AF episode, reason why a brief case report has been included in order to emphasys this point.

Fourthly, grounded on the AFBAR study, we have tried to determine whether LBBB associated with AF had an independent, cumulative effect on mortality for patients without congestive heart failure, in order to assess if a more aggressive therapeutic strategy or closer clinical follow-up should be recommended in this setting. Despite our hypotesys, lack or relationship between LBBB and mortality-morbility has been shown and up until today routinely follow up can be safely recommended in these patients.

Based also on the AFBAR population, we have tried to assess the effect of digoxin on clinical outcomes in patients with AF. Digoxin was not associated with increased all-cause mortality, survival free of admission due to any cause and due to cardiovascular cause, regardless of sex and presence or absence of underlying heart failure.

Unending with the medical treatament of patients with AF we have addressed the rate of AF recurrence, stroke and death during long-term follow-up in a cohort of patients with AF to AFI conversion following treatment with AAD (AAD-AFI) compared with patients with coexisting AF and AFI after radiofrequency catheter ablation of CTI. From our point of view, since the coexistence of these two arrhythmias and the pathological mechanisms underlying them usually go hand-in-hand, evaluation of this so-called “hybrid therapy” (ablation of the CTI and continued pharmacologic therapy with Class I or III AAD) recommended by the ESC guidelines[3], is of crucial importance nowdays, mainly in the current era

where radiofrequency ablation of AF and AFI represent a well-stablished strategy.

Finally, in the last part of this thesis, we have focused on the outcomes in terms of PCM implantation and potential predictors after uneventful successful radiofrequency ablation procedure of typical AFI. This potential risk of auriculoventricular block with the subsequent need of PCM implantation has not been described up to date. However, from a clinical point of view this possibility is very relevant, and as shown before, baseline HR and ECG intraventricular conduction disturbance are simple clinical markers to be taken into account by the physician before and after a CTI ablation. For instance, to start with, these patients could require more cautious monitoring with special attention to the development of syncope, dizziness or dyspnoea. Secondly, it also should be taken into account at the time of the prescription of rate-control drugs that could impair sinus node function or AV conduction.

Next, we will review in detail the most important ideas of the abovementioned studies:

Trends in clinical profile and medical treatments of atrial fibrillation patients over the last 10 years

Based on data obtained from the CARDIOTENS 1999 and CARDIOTENS 2009 we have tried to define trends in AF prevalence and its medical management. We hypothesized that a radical change in the risk profile for thromboembolic events in patients with AF has ensued, as also a change in the use of oral anticoagulants and upstream therapies. The conclusion was that an increase in

the prevalence of AF was observed throught the course of the study. This increase was mainly due to a higher prevalence of AF in patients aged over 70. Interestingly, a more aggressive antithrombotic treatment and radical changes in the use of oral anticoagulants have also been noticed. Comparison of the two registries thus revealed significant shifts in the perception and treatment of patients with atrial fibrillation. We have tried to give some explantations to those results. One possible explanation for the increase in AF prevalence is that today's elderly are a sicker population: advances in preventive medicine and increasing socioeconomic prosperity have resulted in a population of elderly survivors with a higher prevalence of comorbidities including hypertension, diabetes, heart failure, coronary artery disease and prior cardiac surgery, in comparison with their counterparts who lived to a similar age 50 years ago. Nonetheless, as we pointed out in the manuscript, when these risk factors are put into context with the size of the increase in AF prevalence, the relatively small increase in the prevalence of known comorbidities does not appear to offer more than a partial explanation, reason why it is our belief that there must be something else than simply ageing of the population[1]. Hence, these epidemiological studies need to be complemented with further analysis aimed at defining the molecular genetics of AF, in order to provide more insights into the structural and electrical phenotypes resulting from genetic mutations and their interactions with the environment. Otherwise, there is a danger that the burden of this disease could reach epidemic proportions in coming years.

In the present study we have also pointed out that physicians should be aware that we are facing more complex patients, since the elderly have not only the highest risk of stroke among patients with AF, but also the highest risk of

bleeding. Moreover, the herein presented AF population exhibited a higher risk for thromboembolic events, due to the higher prevalence of hypertension, diabetes, previous stroke and heart failure. To our understanding these results are relevant since they indicate a need for new therapeutic strategies, including new oral anticoagulant agents. These agents, which must have a safer drug profile, may provide a useful alternative to current vitamin K antagonists.

It is noteworthy in this study the fact that prevalence of hypertension in patients with AF has also increased in the last decade. Nevertheless, there has been progress in the rate of hypertension control (with a relative increase of 38.5%). This is important because of the emphasis on upstream therapies to slow or halt the progression of AF due to underlying cardiovascular disease and to atrial fibrillation itself. Such agents include ACEIs, ARBs, statins, n-3 (omega-3) polyunsaturated fatty acids, and possibly corticosteroids. As seen in this study, the recommendations reflect the evolution of medical therapeutics in the last 10 years, with a significant increase in the prescription rate of beta-blockers, ACEIs/ARBs and statins. Significant changes were also observed in the choice of ventricular rate control agents throughout the study period. In the 1990s, digoxin was the preferred agent for controlling ventricular rate, but during the study period the use of beta-blockers and CCBs increased significantly, due in part to the growing recognition that digoxin is particularly ineffective at controlling ventricular rate with effort.

To summarize, this comparative analysis of these two large observational, cross-sectional cohort studies has revealed long-term trends in the prevalence and clinical and pharmacological management of patients with AF.

Impact of New Criteria for Anticoagulant Treatment in Atrial Fibrillation

The second study presented here are the results derivated from the CARDIOTENS 2009. The objective of this study was to determine the impact of the new scheme CHA2DS2-VASc and the new recommendations for oral anticoagulation (OAC) in a contemporary sample of patients with AF seen by primary physicians and cardiologists. Our hypothesis was that this new approach would reclassifies a substantial number of patients previously considered ‘‘low’’ or ‘‘moderate’’ risk into higher categories, with the subsequent increase in the indication for OAC. The true magnitude of these recommendations had never been quantified. We found that the new recommendations will result in a significant increase in patients with indications for OAC, at the expense of those previously characterized as low-to-moderate risk. In this cohort, a couple of findings called our attention. Firstly was the fact that the large majority of the study population had a moderate-to-high risk profile for thromboembolic events (77.3% had a CHADS2 ≥2). However, in spite of this, a high percentage of high-risk patients (35%) were not taking anticoagulants. We postulated that contraindications for OAC could partially explain this situation, but also the lack of medical indication and patient compliance due to the need for close monitoring and/or fear of bleeding. Within this subgroup of patients at risk for thromboembolism without OAC therapy, the preferred strategy was monotherapy with acetylsalicylic acid, even though this treatment is less effective than OAC in reducing thromboembolism, both in monotherapy[68] and together with clopidogrel[50]. Furthermore, this treatment also produces high rates of bleeding. Perhaps with new anticoagulant alternatives that are easier to manage, we will be able to mitigate these problems to some

extent, thus increasing the use of OAC in patients for whom this therapy is indicated.

This results are relevant since this strategy is supposed to lead a reduction in the risk of thromboembolic events, but also an increase in the overall number of bleeding events, reason why, now more than ever, it will be crucial to identify this at-risk population, minimizing hece the potential risks inherent to the anticoagulant therapy, especially in the elderly. The new clinical guidelines can also be of help in this regard, as they provide bleeding risk scales that must be taken into account. Current recommendations continue to leave the choice of prescribing OAC or antiplatelet therapy to the physician within a certain range of patients, specifically those with a CHA2DS2-VASc score of 1 (although OAC is recommended). In any case, this will be a much lower percentage of patients (1.8% in our registry) because many patients will have clear indications for anticoagulants in the absence of contraindications.

In this study we sought to warrant that this new suggestions had not gone without detractors who believe that the recommendations set forth are too exhaustive, with no clear benefits demonstrated in randomized clinical trials for each specific scenario, and that the guidelines have been established without conclusive data supporting improved patient prognosis as compared to the previous CHADS2 scale. Although some markers are easy to define, such as age or sex, vascular disease represents a much more diffuse and heterogeneous criterion that can be more difficult to apply to the general population.

Prevalence, Clinical Characteristics and Management of Atrial Fibrillation in Patients With Brugada Syndrome

The third study herein discussed was based on a large cohort of patients with BS collected in a leading Hospital in this field. Taking advantage of the high volume, one of the biggest up today, we aimed to assess the prevalence of AF as the first clinical diagnosis in patients with BS and their demographic and clinical characteristics and diagnosis management in a large cohort of patients. Based on small series and previous case reports, we postulated that a relevat percentage of patients with BS would have AF as first clinical manifestation. Interestingly, this hypothesis was confirmed and we found that AF might be one of the first clinical manifestations of latent BS in a significant number of patients, suggesting that disregarding this association could have tragic consequences. Furthermore, we have tried to highlight the role of the ajmaline test as a useful tool in the diagnostic workup of patients with AF, especially in those with a family history of sudden cardiac death or syncope, regardless of the baseline electrocardiographic findings.

In the study, we have attempted to find explanations to this association. First of all, the mutation in the cardiac sodium channel might exist, not only in ventricular but, most importantly, also in atrial myocytes[85-86], which could be the substrate for reentrant atrial tachyarrhythmias and the increased atrial vulnerability observed in subjects with BS[87]. This could explain, in part, the association between AF and BS. Additionally, it is believed that vagal activity plays an important role in ST-segment elevation and the occurrence of ventricular fibrillation in patients with BS[85]; therefore, it is conceivable that this vagal activity is also related to the initiation of paroxysmal AF[87]. Furthermore,

owing to the presence of a prominent cardiac transient outward potassium current in the atria and the observation that episodes of AF are triggered by closely coupled atrial extrasystoles, it has been postulated that a substrate similar to that responsible for ventricular arrhythmogenesis might underlie the development of AF in patients with BS[88].

To our understanding, these results are crucial since treatment of these patients is subject to relevant changes. First, the prescription of class 1C AADs could prove to be unsafe and should be avoided in these subjects owing to the increased risk of SCD. As a matter of fact, we reported in the abovementioned study, 2 patients with tragic consequences after the initiation of class 1C AADs. Second, identification of these subjects is of great importance due to the subsequent risk stratification of SCD, in line with the avoidance of drugs that could increase the risk of ventricular arrhythmias.

In this study we also try to highlight the role of ajmaline or class IC AAD as a critical step in the diagnostic workup of concealed BS, mainly because it usage is not emphasized in the current European Society of Cardiology/American College of Cardiology/American Heart Association AF guidelines[3]. Our argument is that pathognomonic electrocardiographic changes in BS are dynamic and not reliably reproducible. In our study, 60% of the patients presented with an absolutely normal initial electrocardiogram. Thus, interrogation of the patient's history is absolutely mandatory. In our series, 40% of the patients with AF as the first clinical manifestation of BS, had a positive family history of SCD and 42% had reported previous syncope. This suggests that, regardless of the baseline electrocardiographic findings, the suspicion should mainly be determined by the presence of previous syncopal episodes

and the family history, emphasizing the crucial importance of this easy-to-assess and simple test for improved characterization of potentially affected patients.

Concerning the so-called “pseudo lone AF”, we have also included a case report of a young male patient with paroxysmal AF referred for pulmonary vein isolation following failure of various AAD treatments. Importantly, the electrophysiologic study perfomed during the procedure, before the ablation, showed that it was actually a spontaneous repetitive double nodal response that triggered runs of tachycardia and AF. Following ablation of the slow nodal pathway, the double response and runs of tachycardia disappeared and during follow-up, the patient remained asymptomatic, with stable sinus rhythm and no antiarrhythmic treatment.

In conclusion, in this section, we have tried to highlight that when facing with a patient with AF, a diagnostic work up must be performed in order to rule out potential causes beyond “pulmonare vein firing”, as for instance, BS or slow pathway mediated tachycardia.

Left bundle branch block in atrial fibrillation patients without heart failure.

Based on the AFBAR study (a prospective study carried out by a team of Primary Care physicians in a single health-service) we aimed to determine whether LBBB associated with AF had an independent, cumulative effect on mortality for patients without congestive heart failure in order to evaluate if a more aggressive therapeutic strategy or closer clinical follow-up should be recommended in this setting. We presumed that rate of admissions was higher

than in patients without LBBB. Nevertheless, contrary to our hypothesis, after adjusting for potential confounders, LBBB was not predictive of all-cause death, admission to any cause or cardiovascular cause.

At the time of the study, several series have reported the long-term follow up of patients with AF and rate control. However, little information was available regarding the outcome of AF patients without heart failure and electrocardiographic finding of LBBB. As a matter of fact, it was not specifically collected in the AFFIRM trial[20]. Data coming from the Framingham cohort showed that although QRS duration was not associated with major cardiovascular end points[110], increased QRS duration was associated with an increase in all-cause mortality or cardiac death in patients with LV systolic dysfunction[111]. Recent studies further showed that a prolonged QRS duration was associated with an adverse outcome in HF patients with preserved LVEF and patients with sinus nodal dysfunction with or without HF[112]. Moreover, adverse outcomes in patients with preserved LV systolic function and a prolonged QRS seem to be more common than in systolic heart failure patients without QRS prolongation[102]. In the setting of patients with normal LVEF or those without HF symptoms, a retrospective study reported that progressive increase in QRS duration predicted a poor prognosis in AF patients with preserved LV function[112]. Kruger et al. reported that QRS duration and brain natriuretic peptide levels were independent predictors of LV systolic dysfunction in patients with sinus rhythm or AF[113]. Conversely, results from the AFBAR study did not show that LBBB was predictive of all-cause death. It also failed to show a predictive value for admission due to any cause and admission due to cardiovascular cause. To the best of our knowledge this is the first prospective

study addressing the rate of in hospital admission in patients with AF, LBBB and no signs of HF neither LV dysfunction. On the other hand, the etiology of LBBB in subjects without evidence of structural heart disease is usually an age-related degeneration of the conduction system, which may be either a focal (Lev's disease)[114] or a diffuse (Lenegre's disease)[115] process. Others may have undetected ischemic or valvular heart disease. Whether LBBB is yet another marker that reflects a generalized physiological aging process (for example, diabetes) or is more directly and causally involved in the pathway to cardiovascular death remains unanswered. In any case, LBBB by itself has been related with an adverse prognosis. Accordingly, Fahy et al, based in a screening program (110,000 participants, 112 with LBBB but without apparent or suspected heart disease, mean follow-up of 9,5 years) reported that it was associated with an increase prevalence of cardiovascular disease at follow-up (21% vs 11%; p=0,04)[116]. Nevertheless, population presented here is somehow different to the previous studies above mentioned. On the one hand they are not healthy subjects, but AF patients with associated cardiovascular disease (82,7% with AHT), and as it is known, AF and HF are inextricably linked, as both share common risk factors and each increases the risk of the other. But on the other hand they do not present symptoms of HF or impairment on the ventricular function. In any case, caution must be exercised in this particular population due to several reasons. First of all, the abnormal pattern of ventricular depolarization associated with LBBB can induce or exacerbate systolic and diastolic left ventricular dysfunction and may thus compound the effects of concomitant myocardial disease[117,118]. Secondly, the presence of LBBB increases the risk of developing high-degree atrioventricular block and its

attendant complications after further insults from ischemia, infarction, negatively dromotropic drugs, or age-related conduction-system degeneration. In addition, a prolonged QRS duration may be a marker of cellular uncoupling. Myocardial fibrosis or ischemia-related conduction delay could result in QRS widening and an increased susceptibility to re-entrant tachyarrhythmias[120,121]. Accelerated QRS widening may not only increase electrical instability but also lead to progressive electromechanical remodelling, which may increase the ventricular dyssynchrony. Nevertheless, it must be underlined that prognosis could be different according to the degree of mechanical dyssynchrony induced by the LBBB, and only those patients that achieve a certain amount of mechanical dyssynchrony, may develop symptomatic HF[122]. This could have been one of the reasons that explain the similar outcome in this particular subgroup of patients. Another explanation could have been the fact that the vast majority of patients (85,1%) were under therapy with CEI/ARB agents, something that could have had relevance in the rate of hospitalizations. In the general population of hypertensive patients with AF, results from the LIFE study reported than compared with atenolol, losartan-based therapy improved major cardiovascular outcomes: the occurrence of the primary composite endpoint of cardiovascular mortality, stroke, and myocardial infarction was reduced by 42%, as were its components (42% reduction in cardiovascular death and 45% reduction in stroke), and there was a trend towards lower all-cause mortality. In the Atrial fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events – Irbesartan arm (ACTIVE I) in 9016 patients with AF and risk factors[123], therapy with Irbesartan did not reduce the primary composite endpoint of stroke, myocardial infarction, and vascular death, but significantly reduced

hospitalizations for heart failure. If this is the case in patients with AF and LBBB remains to be elucidated[124], but reassuring results are provided in the present study. Further studies are warranted in order to confirm the presented results. Thus far, in those patients with AF, LBBB without HF under optimal medical treatment, regular follow up could be safely recommended.

"Outcomes of a contemporary sample of patients with atrial fibrillation taking digoxin": Results from the AFBAR study".

Based also on data from the AFBAR study, we aimed to assess and compare the effect of digoxin on clinical outcomes in patients with AF versus those under betablokers (BB) or none. Despite negatives results in previous studies, we hypothesized that digoxine could be an useful drug in a subgroup of patients, without deleterous effect (in terms of cardiovascular mortality and hospital admissions). We found that digoxin was not associated with increased all-cause mortality, survival free of admission due to any cause and due to cardiovascular cause, regardless of sex and presence or absence of underlying heart failure, despite the fact of being patients of higher risk.

Digitalis is the oldest compound in cardiovascular medicine that continues to be used in contemporary clinical practice[125]. While it has beneficial effects in HF and can reduce resting heart rate in AF, some reports have indicated that it use may be an independent risk factor for death[130]. This is particularly relevant nowadays since other safe and inexpensive alternatives such as BB or calcium blockers are readily available. Some studies have been recently published in this field. The RIKS-HIA study[130] and post hoc AFFIRM study[131] showed

increased mortality among digoxin-treated patients. The first one, “The Registry of Information and Knowledge about Swedish Heart Intensive care Admissions” (RIKS-HIA) examined 1-year outcomes from patients on digoxin with AF, CHF, or both, by comparing them to a matched group of patients who were not receiving digoxin. The 4426 patients with AF and no history of HF taking digoxin had a significant increase in the overall mortality (EHR 1.42, 95% CI 1.29–1.56) compared with 16587 controls at discharge (importantly, no such difference was seen in patients with AF and HF, or in patients with heart failure without AF). In the AFBAR study, EHR matched the one describe in the RIKS-HIA, although with wider confidence interval. We cannot rule out that a higher sample size could have translated in narrower confidence interval. However, some differences are notable between both studies. First of all, RISK-HIA was performed in an intensive care setting, which makes it difficult to extrapolate the results. Secondly, It only analyzed total mortality based on a national survey, and finally the follow up was 1 year versus the mean 2,9 years done in the FABAR.

The second one, a recent sub-study of the AFFIRM[131], reported that in patients with AF, digoxin was associated with increased all-cause mortality after controlling for comorbidities and propensity scores, regardless of sex and the presence or absence of underlying HF. Hence, all-cause mortality was 41% higher in patients on digoxin, discouraging in some way rate control with digoxin as a single first line agent. “The Stockholm Cohort study on Atrial Fibrillation (SCAF)”[127], showed that Digoxin is mainly given to an elderly and frailer subset of patients with AF, moreover, when these and other differences in patient characteristics are accounted for, digoxin use appears to be neutral for the long-

term mortality and major cardiovascular events in patients with AF. Consistently, results from the AFBAR study also showed that digoxin is prescribed in high risk patients, even though digoxin appears to have a neutral effect on long-term mortality (EHR 1.42; 95% CI 0.77–2.60, p= 0.2), admission due to any cause (EHR 1,03; 95% CI 0,71-1,49, p= 0,8), and admission due to cardiovascular cause (EHR 1,19; 95% CI 0,72-1,96, p= 0,4), after accounting for age, comorbidity and other patient characteristics. The analysis was consistent when it was performed over the entire cohort (those patients under digoxin, BB, both or none) and when they were divided as those under exclusively digoxin or BB. However, in terms of global survival, the group under BB plus digoxin showed a trend towards a worse outcome than those under BB, digoxin or none. Although no final conclusions can be given in this regard because it is based on a small number of patients (n=58), this is important since it was postulated that beta-blockers could attenuate digoxin's neurohormonal effects. However, when patients were divided as those presenting HF or not, there were no significant differences in relation to the survival between groups. Moreover, this difference could be explained in part because this subgroup represents a frailer subset of patients (higher rate of DM and HF). Anyhow, it's our opinion that it deserves further investigation in order to rule out any kind of causality.

In our study we have tried to highlight the differences between the AFBAR study versus the landmark study performed in the setting of digoxine use; the AFFIRM study[14]. For instance, the AFBAR population was older than the one described in the AFFIRM (74,8 versus 69,7 years old), and also the rate of women (46,9 versus 39,3%) and hypertension (76,58% versus 70,8%). Coronary artery

disease was the predominant cardiac diagnosis in a 17,5% in the AFBAR versus a 26,1% in the AFFIRM. Digoxin was used as monotherapy for rate control in 34,7% in the AFBAR versus 17% in the AFFIRM. The rate of renal disease was 9,6% in the AFBAR and around 5,5% in the AFFIRM. The rate of diabetes mellitus was not specified in the AFFIRM study, but was considerable high in our study population (26,5%). These reasons could explain the differences found in the survival rates (16,5 in the AFFIRM versus 11,9 in the AFBAR) during a similar follow up period (around 3 years in the AFBAR and 3,5 in the AFFIRM).

On the other hand, a comparison between Lenient versus Strict Rate Control II (RACE II) showed that when compared with strict rate control, lenient rate control was not inferior in terms of major clinical events[23]. This could have represented a bias regardless the drug selected, both in the AFFIRM and AFBAR studies. Unfortunately, as we pointed out, strict versus lenient control was not specifically compared in the AFFIRM, although a heart rate of more than 100 beats per minute was found to have an effect on all-cause mortality and cardiovascular mortality (EHR 2.92; 95% CI 2.21–3.85, p= 0.0001 and 2.31; 95% CI 1.53–3.50, p= 0.0001 respectively). Heart rate was not available in our database, thus differences adjusted for heart rate could not be assessed in our study population.

In regard to patients with HF, prior studies with digoxin in patients with chronic HF reported improvements in LVEF[134-135], HF symptoms[136,137] and exercise performance[134]. Despite the fact that the DIG study[140] excluded patients with AF, it was the largest trial that examined the safety of digoxin in patients with HF. Patients were randomized to digoxin versus placebo; digoxin was found to

have a neutral effect on the all-cause mortality (EHR 0.99; 95% CI 0.91–1.07; P = 0.80) but reduced the rate of hospitalizations for HF. Further analysis of the DIG trial data demonstrated that digoxin's beneficial effect only applied to patients in sinus rhyhtm with low serum digoxin drug levels (0.9 ng/mL). It should be highlighted that frequent monitoring of serum digoxin concentrations was performed in the DIG trial. This is relevant because as it is known, positive inotropic and neurohormonal effects are attained with low plasma drug concentrations, and as the DIG trial reported, patients with higher digoxin levels had worse outcomes[140]. Singh Dhaliwal et al, on a cohort of heart failure patients (n=347, 155 of them treated with digoxin), failed to show a reduction in HF hospitalizations or to show any benefit in subgroups of patients with severe LV systolic dysfunction with LVEF < 25% or NYHA class III or IV[141]. Notably, this study population was older, with a higher proportion of patients with NYHA class III or IV HF, and more co-morbid medical conditions, particularly diabetes and hypertension. In the AFBAR study, survival, morbidity and cardiovascular mortality were not higher in those patients with the clinical diagnosis of HF dispensed to digoxin. Of the 95 patients with HF, 29 (30,5%) died during the follow-up period. Digoxin was not associated with all-cause mortality (EHR 0,94; 95% CI 0.20–4,41, p = 0.9), admission due to any cause (EHR 1,02; 95% CI 0,37-2,82, p=0,9) and due to cardiovascular cause (EHR 0,64; CI 95% 0,22-1,86, p=0,4). Consistent with the current evidence, those patients with HF without BB had a significant worse outcome (in terms of hospital admission due to cardiovascular cause) than those under BB, but also than those under digoxin plus BB.

Finally, it should be pointed out that in our study, a sex interaction was not found with digoxin therapy. Post hoc analysis of the Digitalis Investigation Group indicated that digoxin, when used in the treatment of HF, may increase mortality by approximately 20% in women but not in men[142]. Nevertheless, this has not been confirmed in other observational studies. For instance, a study conducted using the Health Information Network population database[143], aimed to study the impact of digoxin exposure on mortality for men and women who carry the diagnosis of HF (n=10808 women), showed absence of a large interaction between digoxin use and sex affecting mortality; Consistent with the AFBAR and the Health Improvement Network Database are two prior observational studies that also did not point out any digoxin sex interaction[144,145]. Because the finding of an interaction from the DIG trial was the result of post hoc analysis, it has been postulated that it could be conceivable that the finding was a type 1 error (false positive) interaction[143], but it is also possible that the DIG trial results were correct, and the observational results are biased by unmeasured confounders that affected the interaction analysis. Besides, it has also been reported that interventions known to reduce mortality in HF are used less in women than in men[143], that although could be due to male and female populations with HF that might legitimately affect prescribing practices, it deserve further investigation.

To sum up, we concluded that, based on the current evidence, there are still doubts regarding the contemporary role of the digoxin, at least in the setting of rate control in patients with AF. Nowadays digoxin is indicated in the current guidelines in patients with heart failure and LV dysfunction, and in sedentary (inactive) patients with a Class of recommendation type “IIC” and a level of

evidence “C”[3]. Evidence in these regards is still a matter of controversy. While sub studies of the AFFIRM[131] raised safety concern, results from the AFBAR study did not show any association between digoxin with increased all-cause mortality and hospital admissions, regardless of sex and the presence or absence of underlying HF. It is our belief that further studies are required in order to ensure the current role of digoxin in the management of patients with AF.

Failure of hybrid therapy for the prevention of long-term recurrence of atrial fibrillation

Based on our consecutive series of patients with typical AFl who successfully underwent radiofrequency catheter ablation at our hospital between November 1998 and May 2010, we tried to determine the long-term effectiveness of the hybrid therapy (management strategy that consists of the ablation of CTI and continued pharmacologic therapy with Class I or III AAD) in the control of AF as well as the differences in clinical outcomes between patients with antiarrhythmic drug AFI, those with coexistent AFI and AF, and isolated AFI. We postulated that this so-called “hybrid therapy”, presently established in the ESC guidelines, is not a very effective therapy for long-term control of AF. The main finding of our study was that a hybrid pharmacological and ablative therapy for AAD-AFI often fails if the follow-up period is sufficiently long, with AF recurring in the majority of the patients (74%, IDR: 19.1/100 person-years). This incidence rate was similar to the recurrence rate of AF in patients with coexistent AFI and AF who underwent CTI ablation (59%, IDR: 19.2/100 person-years). Therefore, the

clinical outcomes and recurrence of AF were similar between Group 1 (AAD-AFl patients) and Group 2 (patients with coexisting AF and AFl). Both of these rates were significantly higher than the occurrence of AF in the isolated AFl group (Group 3) (33%, IDR: 7.9/100 person-years). As we pointed out in the publication, our results are likely to be conservative due to the possibility of hidden asymptomatic recurrences. The EHRA score of AF recurrent episodes in the AAD-AF group was 2.00. Therefore, some of the AF recurrences may not have been detected.

Previous studies have shown hybrid therapy to be an effective method for managing AAD-AFl in the short-term[150-152,155-156]. Reithman et al[153] reported an AF recurrence rate of 20% in AAD-AFl patients during a 8-month follow-up period compared with a 76% recurrence rate in patients with coexistent AF and AFl prior to CTI ablation. Huang et al. reported an AF recurrence rate of 11% in an AAD-AFl series underwent CTI ablation, in a 14-month follow-up period[152], and in the largest series of AAD AFl patients (90 patients), Reithman et al. reported an AF recurrence rate of 27% at 16 months post-ablation and 33% at 21 months post-ablation[151]. Another study reported that AF recurred in 42% of the 72 AAD-AFl included in their study during a 24 month follow-up period, much lower than the recurrence rate of 78% that was detected in a group of patients with prior AF[155]. Given the shorter follow-up times compared with our study, the higher AF recurrence rate observed in our hybrid therapy series[156] could be due at least in part to the longer follow-up period.

In our study, the AF rate was higher during the first 5 years of followup but then continued at a steady rate until the last follow-up time point. In a study with a 5-year follow-up period, Anastasio et al. reported a 90% AF recurrence rate with a

cumulative incidence similar to that found in our series[157]. A study by Turco et al. included 154 AAD-AFI patients who developed AFI after intravenous infusion of 42% during a 2-year follow-up period and 47% during a 4.5-year followup period[158]. In agreement with this result, Hirao et al. reported an AF recurrence rate as low as 25% in a CTI AAD-AFI ablation cohort of 17 patients treated with oral pilsicainide during a 3-year follow-up period[159]. Both figures are extremely low, even lower than the AF recurrence rate in some isolated AFI series[160-163] [15–18]. AAD withdrawal during follow-up may also contribute to the high AF recurrence rate observed in our study. Only 33% of the patients in the AAD-AFI group were receiving AAD treatment at the end of the follow-up period compared with 100% immediately following ablation, and 42% in the coexistent AF group were receiving AAD treatment at the end of the follow-up period compared with 64% immediately following ablation. Nevertheless, AAD withdrawal is unlikely be a determinant factor because a low AF recurrence rate was reported in a study with a short follow-up time period despite the cessation of AAD therapy in 25% of the patients due to adverse effects and a change in AAD treatment in 33% of the patients due to a lack of treatment efficacy[153]. In another series with a 5-year follow-up period, all of the patients continued to receive AAD treatment throughout the study, and the AF recurrence was 90%[157]. Therefore, the AAD effect was modest even in the short-term. In our study, 51% of the patients were in permanent AF 6 years post-ablation.

Differences in the definition of AAD-AFI could also help explain the variation in the reported AF rates. In our study, we only included patients who developed AFI secondary to either intravenous or oral administration of AAD (amiodarone, flecainide and propafenone), and we found the incidence of AAD-AFI to be

6.6%. The study by Anastasio et al. included patients who were initially diagnosed with AF and AFl (15%); the reported incidence of AAD-AFl was 18.4%[157]. Although the definition of AAD-AFl might have contributed to the differences in reported AF recurrence rates, we believe that the length of follow-up is more likely to affect the recurrence rate since the two series with the longest follow-up had similar results[157].

Long-term follow-up and a thorough search for AF (e.g., clinical visits, Holter monitoring, implantable devices, transtelephonic monitoring) are the key factors in determining the real AF recurrence rate after CTI ablation. A study with a 21-month follow-up that used event recorders and 7-day Holter monitoring, reported an AF recurrence rate of 74% in a group of coexistent AF patients who underwent CTI ablation with AAD treatment and an 81% AF recurrence rate for patients who were no longer receiving AAD treatment[165]. This report demonstrates the superiority of pulmonary vein isolation ablation (PVI) with or without CTI ablation compared with CTI ablation alone in patients with coexistent AF and AFl as well as the modest effect of AAD treatment on the AF recurrence rate, although there was a selection bias because the AAD treatment had previously failed in all of the patients included in the study. Even for isolated AFl, combined PVI and CTI ablation has been shown to be more effective than CTI alone (87% vs. 44% of the patients were free of arrhythmia at the end of a 16-month follow-up period with 48 h ambulatory monitoring every 2 months)[165]. In a more recent report, 20 patients with isolated AFl underwent CTI ablation and had a loop recorder implanted. None of these patients was receiving AAD therapy. After 1 year, 42% of the patients had not developed AF and only 9% of patients had symptoms related to AF. An implantable loop

recorder can be effective in the long-term surveillance for AF, although an improvement in the existing technology is needed[166].

In regard to the AFI recurrence, the rate at the end of the follow-up period was 29.6% in Group 1, which is significantly higher than the Group 2 (11.8%) or Group 3 (13%) rate. The AFI recurrence rate in the global population of our study is slightly higher than that reported in the majority of other studies[160-163] . The type of the catheter used might explain some of the differences. In our study, an 8-mm-tip catheter was used in the majority of patients (97.9%), and an irrigated-tip catheter was only used in the remaining 2.1% of the cases. It is known that an irrigated-tip catheter produces greater lesions than an 8-mm-tip catheter[167]. However, we do not have a definitive explanation for the differences in the reported AFI recurrences rates. We do know that in our study, the procedure was performed in sinus rhythm more frequently in Group 1 (55%) than in Group 3 (30%), and the paroxysmal type of AFI was also more frequent in Group 1 (66.7%) than in Group 3 (39.7%). The whole of patients in Group 1 were on AAD therapy. This could give false impression of block in the isthmus in the first ablation.

And important point of our study was that the rate of stroke detected during the follow-up period in Group 1 was similar as the rate seen in Group 2 and a slightly higher stroke rate than Group 3; these results are similar to those reported by others[168-169]. Of note, all of the strokes that resulted in death had transitioned to AF (2 patients in Group 1, 1 in Group 2 and 3 in Group 3), demonstrating the worse prognosis of an AF related stroke[170].

Finally, it is important to highlight that there were a trend towards a lower mortality in AAD-AFI, which was probably related to the younger age and milder

cardiovascular disease in these patients. This trend was maintained even with the development of AF during follow-up despite the fact that AF is a recognized factor of increasing mortality[171-172].

Being aware of the abovementioned limitations, we concluded that AF recurs in most of the patients who receive a hybrid (pharmacological and ablative) therapy, and the clinical outcomes for AAD-AFI patients are similar to those of patients with coexisting prior AF and typical AFI. The efficacy of AAD is modest and can be maintained only in one third of the patients in a long-term follow-up[184].

Risk of pacemaker implantation after uneventful successful cavotricuspid isthmus radiofrequency ablation in patients with common atrial flutter.

In this muliticenter study, we retrospectively reviewed the electrophysiology laboratory database at two Spanish University Hospitals in order to identify patients with AF-AFI who had undergone electrophysiology study for CTI dependent AFI. We hypothesized that in patients with history of CTI ablation for common AFI, ECG Intraventricular conduction disturbance and slow ventricular response at the time of the ablation might be strong predictors of the need of PMI in the long term. As we expected, ECG Intraventricular conduction disturbance and slow ventricular response at the time of the ablation were strong predictors of the need of PMI in the long term. Interestingly, A HR of less than 65 bpm at the time of the ablation was identified as the optimal cut-off value to predict future need of PCM implantation in the follow up[185].

To the best of our knowledge, this is the first study reporting the rate of PMI after CTI ablation in the long term follow up and its relationship with baseline

heart rate and ECG intraventricular conduction disturbance. Not many studies up to date focused in this specific complication in this particular subset of patients with atrial arrhythmias. Sairaku et al[182] reported the rate of pacemaker implantation but immediately after the ablation. They found that 24 patients out of 211 patients (11%) required a permanent PCM implantation for significant SND after AFI termination. In their study, females (OR 2.43; 95% CI 1.32–4.62; p=0.0046), left ventricular ejection fraction (LVEF) < 50% (OR, 2.10; 95% CI 1.20–3.87; p=0.012), and AFI cycle length of > 273 ms (OR, 5.34; 95% CI 3.08 – 10.08; p< 0.0001) were independent predictors of SND requiring PMI. The authors hypothesized that the AFI cycle length could reflect the extent of the atrial remodelling: the more remodelling, the slower the conduction velocity. In our study flutter cycle length was also slower in patients requiring PCM implantation but it was not an independent predictor in the multivariate analysis. Nevertheless, some differences should be mentioned between these two studies. First of all, Sairaku et all[182] focused on the risk of PCM implantation immediately after the ablation. We evaluated the risk of PCM implantation in the long-term follow up, with a noteworthy follow up. Secondly, we took into consideration other reasons for PCM implantation, such as AV conduction disease or slow conducting AF.

From our point of view, it is reasonable to think that patients with slow ventricular response during the AFI could be subtle AV conduction dysfunction; not only physiologic, unmasked by the stress over the AV node impose by the AFI. As a matter of fact, HR at the time of the ablation was an independent predictor for the need of PCM implantation. This risk was particularly higher within the first year after the ablation. Specifically, a HR of less than 65 bpm at

the time of the ablation was identified as the optimal cut-off value to predict need of PCM implantation in the follow up (sensitivity 79% and 74% specificity), regardless of the presence of rate-control drugs. As it is known, although 2:1 A-V conduction is common during AFI, variable A-V conduction (e.g., 4:1 or 6:1) can be seen frequently, but at the present time there is lack of evidence regarding the level of block in these situations. On the one hand, Josephson and co-workers reported that block below the His can also be observed, but on the other hand the same group stated that intra- or infra-His block during atrial flutter is usually physiologic because refractoriness in the His-Purkinje system exceeds the flutter cycle length[183]. Unfortunately due to retrospective characteristic of our study we could not evaluate the level of the block so it cannot be concluded whether the risk of PCM implantation depends on its level. However, based on the fact that more that half of the patients requiring PCM implantation presented some degree of intraventricular conduction disturbance in the baseline ECG, it could be suggested, as a hypothesis, that the level of the block could have played a role. In any case, it is our opinion that from a clinical point of view, baseline HR and ECG Intraventricular conduction disturbance could be simple clinical markers to be taken into account by the physician since management of these patients is subject to relevant changes. For instance, to start with, these patients could require more cautious monitoring with special attention to the development of syncope, dizziness or dyspnoea. Secondly, it also should be taken into account at the time of the prescription of rate-control drugs that could impair sinus node function or AV conduction.

As aforementioned some limitations in the study merit comment. First, retrospective multicentre study design increased the risk for bias and

confounding. However, consecutive patients who underwent CTI radiofrequency ablation were included and follow-up was performed according to a uniform protocol. Moreover, the non-randomize nature of the study does not allow us to conclude which strategy (ablate or pace) should be chosen in this subgroup of patients. Probably, it could be hypothesized that restoration of sinus rhythm could be beneficial for the AV synchrony and the potential thromboembolic risk of the atrial flutter. But it is our opinion that these points should be specifically addressed in futures studies. Secondly, we have enrolled patients with 'persistent' AFI; had it been performed in patients with shorter AFI duration, the degree of remodelling may have been less with the potential repercussion over the right atrium and the sinus node function. However, the duration of persistent or chronic AFI may be at times difficult to define accurately due to the misinterpretation of the symptoms. Thirdly, as it is already known, AFI cycle length is affected by the autonomic tone. Therefore, not conducting an autonomic blockade was a major limitation of our study. On the other hand, although patients who presented complete auriculoventricular block by an inadvertent application of energy on the normal AV conduction system were excluded, we cannot rule out the damage of the AV conduction system during the RF applications. Furthermore, coronary angiography was not performed in those patients so it cannot be excluded intended and unidentified damage of the right coronary artery during the application.

Heart rate measurement may not reflect the heart rate range or average heart rate of the patient and may be too crude to be a reliable indicator of risk.

Finally, patients who had a previous PCM were not included in our study. This possibly led to underestimating the prevalence of the coexistence of sustained

AFI and clinically significant SND or AV conduction disease. Subsequently, further studies with more number of patients and events will be needed in order to ascertain the real relevance and management of the problem.

All in all, with this study, we highlighted the important association between baseline ECG intraventricular conduction disturbance and heart rate pre ablation and the subsequent risk of PCM implantation. However, this point is not mentioned in the current recommendations for the management of patients with AF – AFI. As a matter of fact although both diseases share the same recommendations[3], some intrinsic differences between both substrates are present. Hence, in light of our major finding, therefore, assessing it prior to ablation can be helpful for the risk stratification of SND or AV conducting disease requiring a PCM implantation in patients with persistent AFI.

CONCLUSIONS

- AF prevalence has increased over the last decade. This increase is due to the higher prevalence of AF in people over 70 years old. Moreover, the current AF population exhibits a higher risk profile for thromboembolic events because of the higher prevalence of hypertension, diabetes, CAD, LVH, previous stroke and HF. Regarding medical treatment, firstly more aggressive antithrombotic treatment has been observed, as well as radical changes in the use of oral anticoagulants, reversing the decreasing use in elderly patients observed in 1999.
- The new recommendations (CHADASVASc versus $CHADS_2$) will result in a significant increase in patients with indications for OAC, at the expense of those previously characterized as low-to-moderate risk.
- AF could be one of the first clinical manifestations of latent BS in a considerable number of patients. In this setting, ajmaline challenge plays an essential role, mainly in young patients with a family history of sudden death, despite having normal findings on a baseline electrocardiogram.
- In AF patients without HF nor LV dysfunction, after adjusting for potential confounders, LBBB was not predictive of all-cause death, admission to any cause or cardiovascular cause.
- Digoxin was not associated with increased all-cause mortality, survival free of admission due to any cause and due to cardiovascular cause, regardless of gender and presence or absence of underlying HF, despite the fact of being patients of higher risk.
- AF recurs in most of the patients who receive a hybrid (pharmacological and ablative) therapy, and the clinical outcomes for AAD-AFI patients are similar

to those of patients with coexisting prior AF and typical AFI. The efficacy of AAD is modest and can be maintained only in one third of the patients in a long-term follow-up.

- In our non-trial-based cohort of patients with a history of CTI ablation for common AFI, ECG intraventricular conduction disturbance and slow ventricular response at the time of the ablation were strong predictors of the need of PCM implantation in the long term. A heart rate of less than 65 bpm at the time of the ablation was identified as the optimal cut-off value to predict future need of PCM implantation in the follow-up.

CONCLUSIONES

- La prevalencia de FA ha aumentado significativamente en la última década. Este incremento es a costa principalmente de pacientes de más de 70 años. Además, la población actual representa un mayor perfil de riesgo de eventos tromaboembólicos debido a una mayor presencia de hipertensión arterial, diabetes mellitus, enfermedad coronaria, hipertrofia ventricular izquierda, accidentes cerebrovasculares e insuficiencia cardiaca. En lo referente al tratamiento médico, se aprecia un aumento en el uso de los fármacos anticoagulantes y una disminución en el uso de antiagregantes.
- Las nuevas recomendaciones (CHADASVASc versus $CHADS_2$) resultarán en un incremento significativo en las indicaciones de anticoagulación oral, a expensas de aquellos previamente caracterizados como de riesgo bajo-moderado.
- La FA puede ser una de las primeras manifestaciones clínicas en pacientes con un síndrome de Brugada latente. Por lo tanto el test de ajmalina puede desempeñar un papel fundamental, principalmente en sujetos jóvenes con historia de muerte súbita, a pesar de presentar un electrocardiograma basal normal.
- En pacientes con FA sin insuficiencia cardiaca ni disfunción ventricular izquierda, despues de ajustar por posibles factores confusores, el bloqueo de rama izquierda no es predictor de mortalidad de cualquier causa, ingresos de cualquier causa ni de causa cardiovascular.
- En pacientes con FA, la digoxina no se asocia con un incremento de la mortalidad de cualquier causa ni de causa cardiovascular,

independientemente del sexo y la presencia de insuficiencia cardiaca, a pesar de ser éstos pacientes de más alto riesgo.

- En pacientes con FA que desarrollan un fluter auricular *tipo IC*, la estrategia híbrida (ablación del istmo cavotricuspídeo y mantenimiento de los fármacos antiarrítmicos) se asocia con una alta recurrencia de la FA (dos tercios de los pacientes), por lo que debería valorarse en este contecto la ablación combinada del istmo cavotricuspídeo y de venas pulmonares.
- En pacientes con FA/flutter auricular e historia de ablación del istmo cavotricuspídeo, la presencia de trastornos de la conducción intraventricular basal y una baja frecuencia cardiaca al momento del implante (en concreto flutter auricular con respuesta ventricular < de 65 lpm) son predictores significativos de requerimiento de implante de marcapasos durante el seguimiento post ablación.

SUMMARY

SUMMARY - RESUMEN

En la presente tesis se intentan evaluar aspectos importantes a nuestro parecer referentes al manejo integral de los pacientes con fibrilación auricular (FA) que actualmente no están contemplados en las guías de prática clínica. Para elaborar dichas observaciones nos hemos apoyado en diferentes bases de datos de pacientes con FA, nacionales e internacionales que nos han llevado a publicar dichos resultados en revistas médicas.

En primer lugar y casi a modo de introducción de los resultados que se presentan posteriormente consideramos relevante evaluar la tendencia en la prevalencia y el manejo farmacológico de los pacientes con FA en la última década. Para ellos nos basamos en dos estudios transversales realizados el primero de ellos en 1999 y el segundo en 2009. Dicho estudio parece indicar que la incidencia de FA ha aumentado significativamente en la última década. Además, la población con FA muestra un perfil de riesgo tromboembolico más adverso (mayor prevalencia de hipertensión arterial, diabetes mellitus, enfermedad coronaria, hipertrofia ventricular izquierda, ictus previos e insuficiencia cardiaca). Esto ha llevado entre otros motivos a un cambios radical en el uso de fármacos anticoagulantes y antiagregantes. A su vez, dado el cambio en las recomendaciones para la estratificación del riesgo tromboembólico (CHADASVASc versus $CHADS_2$), pretendimos evaluar en la misma población la relevancia que en nuestro medio tendrá dicha recomendación a la hora de prescribir fármacos anticoagulantes. El resultado de dicho estudio indica que esta nueva escala supondrá un incremento notable en la indicación de anticoagulación oral a costa fundamentalmente del subgrupo de pacientes catalogados previamente

como de riesgo bajo-moderado. Por lo tanto, es nuestra opinion que la evaluación del riesgo hemorrágico deberá ser tenido en cuenta ahora más que nunca para prevenir los efectos colaterales que supone el incremento en la prescripción de anticoagulantes orales en base a las nuevas recomendaciones.

Dejando a un lado la epidemiología de la enfermedad, nos centramos posteriormente en la etiología de la FA. Numerosas causas han sido atribuidas en la génesis de la FA y aparecen consecuentemente detalladas en las guías de práctica clínica. Sin embargo la presencia de una canalopatía latente (síndrome de Brugada) con la consiguiente vulnerabilidad auricular no aparece mencionada entre ellas. Para nostros esta relación representa un cuestión crucial puesto que en dicho caso el tratamiento farmacológico y el abordaje del paciente (y familiares) es completamente diferente al manejo de los pacientes con FA “solitaria” o secundaria a otras causas. Por lo tanto, en base a los resultados de nuestro estudio en el que se registró que una pequeña proporción de pacientes con FA presentan síndrome de Brugada latente, nosotros abogamos por la realización de test de bloqueantes de los canales de sodio en pacientes con fibrilación auricular jóvenes sin causa aparante, y especialmente cuando presentan antecedentes familiares de muerte súbita.

Independientemente de la etiología también nos pareció relavante abordar la cuestión de cual es la relevancia de la presencia de bloqueo de rama izquierda en pacientes con FA y sin disfunción ventricular izquierda. Hasta la fecha no se ha evaluado dicho aspecto lo cual es relevante a la hora de establecer como planear el seguimiento de estos pacientes. En nuestra

población, tras ajustar por potenciales factores confusores, la presencia de bloqueo de rama izquierda no fue predictor de mortalidad de cualquier causa, hospitalización de origen cardiovascular o de cualquier causa.

Centrándonos posteriormente en el tratamiento farmacológico de los pacientes con FA, creemos que es relevante evaluar (por primera vez) en nuestro medio la seguridad de la digoxina en éste ámbito. Dicho fármaco ha sido cuestionado recientemente en subanálisis de estudios de pacientes con FA y en pequeños estudios retrospectivos/meta-análisis. Cuando nosotros lo evaluamos de forma prospectiva en nuestra muestra de pacientes con FA seguidos durante 3 años, dicha medicación, a pesar de prescribirse en pacientes más añosos y sedentarios, no se asoció con muerte de cualquier causa ni supervivencia libre de ingresos hospitalarios (tanto de causa cardiovascular como de cualquier causa). Por lo tanto creemos que aunque es cierto que hay que prestar atención a ciertas peculiaridades propias de dicha droga, en nuestro estudio no parece haber evidencia que obligue a desterrar esta medicación del arsenal terapeútico de pacientes con FA. También en linea con el tratamiento farmacológico creímos conveniente evaluar la efectividad del tratamiento híbrido (farmacológico y ablación del istmo cavotricuspídeo) en nuestra muestra de pacientes con flutter auricular secundario a tratamiento antiarrítmico prescrito para control de la FA. Cuando se atendió a la tasa de eventos (FA, ictus, muerte) la tasa de los mismos fue similar a aquellos pacientes con FA sin flutter auricular. Estos restultados desde nuestro punto de vista suponen un cambio importante a la hora de manejar estos pacientes con flutter auricular secundario a fármacos

antiarrítmicos y tal vez la ablación combinada de ICT y FA sea más apropiada en este contexto.

Finalmente pretendímos evaluar en dicha población de pacientes remitidos para ablación del ICT la tasa de requerimiento de implante de marcapasos post procedimiento. En dicha muestra apreciamos que la presencia de trastornos de la conducción intraventricular y una frecuencia cardiaca inferior a 65 lpm son significativos predictores de requerimiento de marcapasos post ablación. Esto es relevante a la hora de prescribir fármacos que puedan disminuir la respuesta ventricular así como planear los posteriores controles post ablación.

En suma, en el presente trabajamo hemos intentado evaular de forma integral (epidemiología, etiología y tratamiento) aspectos relevantes para el manejo de pacientes con FA-flutter auricular no recogidas en las actuales guías de práctica clínica pero que desde nuestro punto de vista son relevantes y deben ser tenidas en cuenta por todos aquellos profesionales que traten con pacientes afectos por esta cada vez más prevalente enfermedad.

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