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Joint Mexican Position Document on the Treatment of Atrial Fibrillation

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Posicionamiento conjunto acerca del tratamiento para fibrilación auricular

Avalado por: Asociación Nacional de Cardiólogos de México (ANCAM), Sociedad Mexicana de Electrofisiología y Estimulación Cardiaca (SOMEEC) y Sociedad Mexicana de Cardiología (SMC).

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I. WHAT IS KNOWN ABOUT THE EPIDEMIOLOGY OF ATRIAL FIBRILLATION IN MEXICO? CAN IT BE CONSIDERED A PUBLIC HEALTH PROBLEM?

Atrial fibrillation (AF) incidence and prevalence increase with age. Its prevalence is near to 2% in the general population, but it could be as high as 10% in those over 75 years.[1,2] Before the Mexican Registry of Atrial Fibrillation (ReMeFA) was published a market study was conducted in Mexico in 2007, finding that, for a population of 105,338,982 people the prevalence of cardiac arrhythmias was 2.4%, with tachyarrhythmias being the most common with 56% (1,402,453 people), of which, AF was the most frequent arrhythmia, occupying 60.7% of tachycardias (or a total of 851,489 cases).[3]

Today, we estimate that in Mexico, there are more than one and a half million people with AF, with a prevalence ranging from 0.43% in the 40-49 age group to 8.48% in those over 80 years old, for an average of 1.58% in a population over 40 years of age.[3] Permanent or chronic AF represents 51.5% (corresponding to 438,134, Mexicans). The ReMeFA[4] study was the first national multicenter registry, with clinical follow-up of one year, in 1,201 subjects, on the comparison of AF treatment with a rhythm control strategy or with rate control. This study was carried out with the collaboration of 71 cardiologists and electrophysiologists. At one year follow-up, an incidence of 3% of ischemic cerebral vascular disease (CVD) was observed in the rate-control strategy, significantly higher than 1% in the rhythm control strategy ($p = 0.04$).[2] Worldwide, CVD is the second leading cause of death and the leading cause of disability.[1] CVD has become a health problem as a result of increased life expectancy and lifestyle changes, representing one of the leading causes of death in Mexico.[2,3] According to the Brain Attack Surveillance project in Durango, it is estimated that in Mexico the annual incidence of CVD is 232.3 cases per 100,000 inhabitants over 35 years of age, while its prevalence is eight cases of CVD per 1,000 inhabitants, a figure that increases to 18 cases per 1,000 in people over 65 years of age.[5] It is important to note that in recent years, CVD has occurred in younger people as a result of the continuing increase in risk factors, including unhealthy lifestyles and obesity. In a Pan American Health Organization report, indicators of premature vascular mortality (in people under 70) showed that in

Mexico the rate in non-diabetics was 10.7 per 100,000, compared to 3.3 and 5 per 100,000 in Canada and the USA, respectively.[6] Based on these results, we consider AF to be the most frequent tachyarrhythmia in Mexico with a high percentage of cerebral vascular disease, so it should be considered a public health problem in Mexico.[6]

I a. Importance of early diagnosis

AF is an independent risk factor associated with mortality, increasing it twice in men and 1.5 times in women;[1] mortality due to embolic events can decrease with oral anticoagulation but other causes of cardiovascular death such as heart failure or sudden death continue to be frequent despite adequate treatment, that is the reason why an early diagnosis is of utmost importance since AF can be asymptomatic (silent AF), and patients have it inadvertently, delaying proper treatment. The diagnosis of AF requires an event lasting at least 30 s and to be observed on an ECG, rhythm strip, or cardiac monitor, characteristically with the irregularity of RR intervals without clearly identifiable P waves or with visible «f» waves of fibrillation. An early electrocardiographic recording is cost-effective for documenting chronic forms of AF particularly in populations older than 65 years with a prevalence of up to 2.3%, obtaining a «necessary to treat number» of 70 to find one person with AF.[1] As for paroxysmal AF, the longer the record, the more likely it is to find silent events. Now the technology has evolved, so in Mexico, we already have 48-hour recorders and implantable loop recorders whose duration is up to three years. The more we use these devices in high-risk patients, more likely to find AF and being able to start appropriate treatment earlier.[4]

II. ANTIARRHYTHMICS AVAILABLE IN MEXICO FOR RHYTHM CONTROL: HOW AND WHEN?

II a. Recent onset atrial fibrillation: conversion to sinus rhythm in an unstable patient

If the AF paroxysm is associated with «angina pectoris», pulmonary edema, low blood pressure or shock, urgent electrical cardioversion should be practiced. It is recommended that the shock should be administered with the highest available energy: 200 joules biphasic or 360 joules monophasic. It is not suggested to proceed in stages by increasing from lower energies. The reason for this is to reduce the number of shocks, use a lower cumulative dose of energy, and reduce the anesthetic time. For thromboembolic prophylaxis, unfractionated heparin (bolus according to body weight followed by infusion) should be administered, followed by oral anticoagulation.[1] Although embolism risk might be increased because of the emergency nature of the condition.

II b. Stable patient

Assuming that the corresponding thromboembolic prevention measures have been taken and that the heart rate is controlled with the isolated or combined use of beta-blockers, calcium channel blockers or digoxin, the clinician should assess whether it is reasonable to administer any antiarrhythmic drug to restore sinus rhythm. It is known that up to 50% of AF paroxysms may spontaneously remit within 24-48 hours.[7] If AF persists after this period, pharmacological cardioversion with amiodarone (oral or preferably intravenous), propafenone or flecainide is indicated. Intravenous amiodarone is given at a loading dose of 5 to 7 mg/kg in 30-60 minutes, followed by a maintenance dose of 1.2 to 1.8 g/day until ten g[1] completed. The oral dose of propafenone is 600 mg in a single dose, and that of flecainide is 300 mg in a single dose. Sinus rhythm conversion occurs in 80-90% of cases within the first few hours.[8] It should be emphasized that sotalol, dronedarone, and digoxin are not indicated for conversion to sinus rhythm. If the episode becomes persistent despite the use of antiarrhythmics, electrical CV is indicated, preceded by a transesophageal echocardiogram to rule out intracavitary thrombus.[1,9]

II c. Maintaining sinus rhythm

Once the conversion to sinus rhythm has been achieved, the clinician should assess whether

it is appropriate to use an antiarrhythmic daily for the maintenance of sinus rhythm or whether it is preferable not to give preventive antiarrhythmic and choose to treat the episode with the «pill in your pocket» strategy.[1,10] For the maintenance of sinus rhythm it is indicated to use one of the following antiarrhythmics: propafenone, flecainide, sotalol, dronedarone or amiodarone. In the absence of structural heart disease, the use of propafenone or flecainide is recommended.[10] Sotalol may be used in the presence of ischemic heart disease. Dronedarone is indicated only for cases of paroxysmal AF, in the absence of heart disease and with preserved left ventricular ejection fraction. Amiodarone is considered a second-line drug due to its side effects; however, it is the most effective alternative for maintaining sinus rhythm.[1] In the case of heart failure, the use of amiodarone is recommended. For the last three drugs (sotalol, dronedarone, and amiodarone), the duration of the QT interval should be monitored.[11] A single dose of 600 mg propafenone or 300 mg flecainide is recommended for the «pill in your pocket» strategy.[1,8,10] Caution should be exercised due to the possibility that these two drugs may unmask the electrocardiographic signs of Brugada syndrome or convert atrial fibrillation into an atrial flutter with a paradoxical increase in ventricular response (less than 1% of cases).[12]

II d. Recurrent atrial fibrillation (paroxysmal, persistent)

Unlike the first episode approach (or very sporadic recurrent cases), for recurrent cases of paroxysmal and persistent presentation, it is indicated to use antiarrhythmics for prevention. The therapeutic options are propafenone, flecainide, sotalol, dronedarone, and amiodarone. It should be emphasized that dronedarone is only indicated to prevent recurrence of paroxysmal or persistent AF that has lasted less than six months of evolution, in the absence of heart disease and with preserved left ventricular ejection fraction. AF ablation (radiofrequency or cryoballoon energy) should be considered as a first-line alternative for drug-refractory or symptomatic cases (at least one antiarrhythmic class Ic or III).[1,13]

II e. Persistent atrial fibrillation (lasting more than a year)

This category was established to identify patients who may not benefit from a rhythm control strategy because AF is permanent, from those with a chance to convert to sinus rhythm. There are two therapeutic options: 1) facilitated electrical cardioversion with prior use of antiarrhythmics[14] and 2) AF ablation.[1] It is reasonable to proceed with facilitated electrical cardioversion with antiarrhythmic drugs as the first measure because if successful, although with early relapse, it demonstrates that the patient can maintain sinus rhythm and would be a suitable candidate for catheter ablation.[1,13,14]

II f. Immediate post-cardioversion recurrence

Electrical cardioversion is one of the cornerstones for rhythm control in AF. However, immediate recurrence or therapeutic failure, described in up to 26% of cases, limits its clinical application.[15] To increase the response rate, antiarrhythmics must be given before the electric shock.[13,14] The use of verapamil, amiodarone, or sotalol has been reported to decrease the incidence of immediate recurrence.[13-16] Other drugs such as ibutilide (not widely available in Mexico), vernakalant (not available in Mexico), and ranolazine (available in our country) have also shown benefit in this area.[1,17]

II g. Delayed cardioversion (facilitated by antiarrhythmic)

It is indicated for persistent AF, mainly when the temporal progression is unknown or when a high probability of immediate recurrence is assumed. Amiodarone 600 mg per day administered for one month (total dose 16.8 g) is indicated for a better outcome. Pharmacological cardioversion has been observed to occur during loading dose in 16-18% of cases.[1] The success of electrical cardioversion is 88%. Besides, if cardioversion does not occur, the ventricular response of the heart rate during AF could be reduced (from 100 ± 25 to 87 ± 27.5 beats per minute [$p \leq 0.001$]) by a negative dromotropic effect on the atrioventricular node.[18]

III. HOW TO MANAGE VENTRICULAR RATE CONTROL IN PERMANENT AF? WHAT IS THE ROLE OF AV NODE ABLATION WITH PACEMAKER IMPLANT?

Much that has been said about AF can be summed in three brief sentences: it is the most common arrhythmia, the easiest to diagnose and the most difficult to treat.[19-21] Another no less ominous peculiarity is that AF is a progressive disease,[22] and that it is a condition that contributes to its perpetuation.[23] In other words, the sooner we try to revert and achieve sinus rhythm, the higher the chances of success (to keep the patient in sinus rhythm).[24]

III a. Permanent (chronic) AF

Permanent AF is the one in which recovery of sinus rhythm is not possible.[1,19] The distinguishing feature of this phase of AF is the uncontrollable variability of the ventricular rate. It depends on the AV conduction and not on the sinus node function; it is the autonomic nervous system (sympathetic and vagal) that determines the AV conduction velocity and thus the ventricular frequency.[25] It is common to consider ventricular frequency analysis only with a resting electrocardiogram (EKG) record, however this is not quite right because of the circadian heart rate variations. On the other hand, vagal tone during the early morning hours can delay AV conduction and cause considerable and sufficient ventricular pauses to cause low brain perfusion with its consequences. The therapeutic possibilities are: pharmacological and interventional.[26,27]

III b. Pharmacological treatment

The main limitation of drugs comes from their AV node conduction slowing properties, thus inducing severe bradycardias without avoiding abnormally fast rates.[28] Antiarrhythmic drugs such as amiodarone are ineffective, as, by definition, sinus rhythm is not intended to be restored.[29] Beta-adrenergic blockers may delay AV conduction, but decrease the force of ventricular contraction.[1]

III c. Interventional treatment

Once it has been demonstrated that the patient has a very high ventricular rate variability and maintains a heart rate above 140/min, heart failure is an imminent threat,[1,30] Ablation of the AV junction and placement of a variable frequency ventricular pacemaker (VVIR) is the indicated option. The use of anticoagulants is imperative even in patients who have regained sinus rhythm after isolating the pulmonary veins, so there is no argument to avoid it.[31,32] Radiofrequency thermal injury of the AV junction causes an irreversible blockage. The injured tissue can be the AV node or the His bundle, and can be achieved either from the tricuspid ring or from the left ventricle.[1] The success of this procedure is very close to 100%, and the possibility of recurrence is practically null. The placement of a ventricular pacemaker is a routine procedure in any institution, with low risk and ventricular function improved by obtaining regularity of rate.[1]

In a series of patients from the Department of Experimental Medicine and Arrhythmias (UNAM) in the General Hospital of Mexico, 177 ablations of the AV junction with placement of a ventricular pacemaker have been carried out. All patients showed a ventricular rate variability greater than 140 bpm, when the normal is above 100 bpm. Many of them, during the 6-min walk test (6MWT), could not perform more than 250 meters. In 159 of the patients, ablation of the AV junction was achieved from the right atrium, and in 17 (10%) it had to be done from the left ventricle. In no case, there was a recovery of AV conduction. (unpublished data). This study concludes that ablation of the AV node is affordable and feasible in cases of permanent AF. Isolation of pulmonary veins should not be performed as an attempt to recover sinus rhythm, even if other options have been exhausted. Anticoagulation is mandatory in almost all patients with AF, regardless of its type.

IV. WHAT IS THE CLINICAL BENEFIT AND WHAT IS THE PURPOSE OF PULMONARY VEINS ISOLATION IN AF?

In general, there is no definitive cure for AF; the therapeutic goal is to control symptoms, delay

disease progression, and prevent a cardiovascular event.[33] Electrical isolation of the pulmonary veins when there is recurrence with drug treatment is the most effective strategy for maintaining sinus rhythm and keeping the individual asymptomatic.[1,33] Invasive electrophysiological treatment is relatively recent; it began when it was discovered that premature atrial contractions from the pulmonary veins were responsible for initiating AF; which led to the establishment of the selective elimination of these ectopic foci as a therapeutic goal.[33] Currently, the strategy is broader, trying to make electrical isolation of all pulmonary veins, from the antrum and not from the ostium to avoid side effects such as pulmonary stenosis. Other cases with a more advanced disease require different ablation strategies such as supplemental lesion in the left or right atrium, or even both, as well as in the superior vena cava or cavotricuspid istmus.[1,33] AF is a progressive disease, starting with tachycardia of the pulmonary veins (they usually arise from there, but they can be originated in other sites) that initiates AF; however, AF produces more AF with a remodeling, not only anatomical but also electrical process of the atria. If AF is prolonged enough, it becomes a biatrial disease with fibrosis, electrical remodeling, and dilation of both atria that causes rotor systems that support it, making it finally permanent.[34-36] Technology and knowledge have evolved, thus, 74% of the patients submitted for radiofrequency catheter ablation have sinus rhytm at a one-year follow-up.[1,33] AF ablation is recommended in paroxysmal, persistent and long standing persistent AF refractory or intolerant to antiarrhythmic drugs; it may also be considered as the first line in symptomatic paroxysmal AF.[1] The therapeutic objective it is to create a series of lesions that prevent AF starting by eliminating the triggering extrasystoles or modifying the substrate that maintains it.[1,33] Currently, ablation strategies depend on the type of AF; if it is paroxysmal AF, the success rate is higher, since the isolation of the pulmonary veins is sufficient to maintain sinus rhythm.[1,33] On the other hand, if it is persistent AF, the success rates are lower; in these cases the therapeutic strategy is broader, requiring different ablation lines and searching for rotors not only in the left atrium but also in the right atrium, and even in other thoracic veins such as the coronary sinus, caval veins or Marshall's vein.[1,33,36] This complexity leads to a significant reduction of the long-term success rate, requiring two or more procedures to make it more likely that the patient maintains sinus rhythm. Because of these results, patients with paroxysmal AF are now preferred for early intervention. Scientific evidence shows that the main prognostic factor for maintaining sinus rhythm is achieving complete electrical isolation of the pulmonary veins. In advancing stages the posterior wall, also plays an essential role in the maintenance of sinus rhythm, as a therapeutic goal.[1,33,34] The techniques employed can be two, with RFCA by using irrigation catheters or with cryoballoon ablation (CBA); the latter was limited only for paroxysmal AF, but nowadays, it is safe to perform it in persistent AF with the advantage of being a less operator-dependent procedure, with a faster learning curve and above all, fewer complications than RFCA,[1] with comparable results in comparative studies.[1,33,37] In centers of high experience, it can give results of up to 85% of patients free of AF at follow-up in 12 months.[38] In Mexico, in the series published by the *Instituto Nacional de Cardiología*[39] *(Clínicas Mexicanas de Cardiología)* of RFCA, in a period of eight years, in patients with paroxysmal AF, there is a 78% success rate at a 12-month follow-up in a total of 121 patients. CBA in the first experience in Mexico from 2013-2014 in a multicenter study (unpublished data, from *Hospital Ángeles Interlomas, CMN Siglo XXI, CMN 20 de Noviembre* and *Servicios de Salud del Estado de Puebla*) with 52 patients, exclusively with paroxysmal AF, the CBA was successful in 78% of cases with an 18-month follow-up.

V. WHEN AND HOW SHOULD ANTITHROMBOTIC PROPHYLAXIS BE GIVEN IN THE SUBJECT WITH ATRIAL FIBRILLATION? ANTI-PLATELET DRUGS, VITAMIN K ANTAGONISTS, DIRECT ORAL ANTICOAGULANTS, AND LEFT ATRIAL APPENDAGE OCCLUDERS

V a. AF is a cause of stroke

The presence of AF has long been associated with the development of cerebral and systemic

(pulmonary, limb, coronary, renal and visceral) embolism.[40] Initially, only AF secondary to valvular disease, usually rheumatic heart disease, was considered thrombogenic,[41] but since the Framingham study, AF of non-rheumatic origin is also recognized as a cause of embolism.[42]

V b. The prevention of embolisms in «valvular» AF should be performed with vitamin K antagonists (VKA)

For embolic risk purposes, «valvular» AF is considered to be the one associated with moderate or severe mitral stenosis or in the presence of a mechanical valve prosthesis.[43] Although acetylsalicylic acid (ASA) was initially used in patients with rheumatic heart disease,[44] subjects with valvular AF should now be anticoagulated with VKA, either acenocoumarin or warfarin.[1,45] The dose is that necessary to achieve an INR between 2.0 and 3.0, except for patients with mechanical valve prostheses that require INR between 2.5 and 3.5. Direct oral anticoagulants (DOAC) should not be used in valvular AF until the results of studies supporting this practice are available.[46] To improve the time in therapeutic intervals it is recommended to: 1) establish anticoagulation clinics[47] and 2) self-monitoring of the INR with portable devices.[48]

V c. CHA_2DS_2-VASc score and options for prevention of embolisms in «non-valvular» AF

For patients with AF not associated with mitral stenosis or a mechanical valve prosthesis, a choice can be made between antiplatelet drugs, VKA or DOAC. Antiplatelet agents have the weakest effect in preventing embolism.[49] In a meta-analysis of randomized studies (Hart RG et al), the relative risk reduction of stroke with ASA compared to placebo was calculated at 19% while with VKA was 64%.[50] It is important to note that based on the results of the ACTIVE-W study, dual antiagreggation therapy (e.g. ASA and clopidogrel) is not recommended over oral anticoagulation.[51]

The decision of which drug should be used in the prevention of cerebral infarction can be based on the use of the CHA_2DS_2-VASc[1,52] score *(Table 1)*. For individuals with no points, (no risk factors, considered «low risk» by not observing any embolic event in a follow-up year) it is possible to choose: not

Table 1: Risk factors for cerebral infarction included in the «CHA_2DS_2-VASc» score and hemorrhagic risk factors included in the «HAS-BLED» score.

CHA_2DS_2-VASc	Score	HAS-BLED	Score
C (*congestive heart failure*) = left-sided heart failure	1	H = hypertension	1
H = Hypertension	1	A = impaired liver or kidney function	1 each
A (*Age*) = ≥ 75 years	2	S (*Stroke*) = cerebral vascular disease	1
A (*Age*) = age 65 to 74 years	1	B (*Bleeding*) = bleeding	1
D-diabetes mellitus	1	L (*Labile INR*) = highly variable INR (outside therapeutic intervals)	1
S (*Stroke*) = previous stroke	2	E (*Elderly*)	1
S = Sex category	1	D (*Drugs*) = drugs or alcohol	1 each
V = peripheral vascular disease		1	
Risk of cerebral infarction:		Risk of bleeding in patients with AF with indication of oral anticoagulation:	
• Low = 0 • Intermediate = 1 • High = 2		• Low = 0 • Intermediate = 1-2 • High = 3 or more	

to give treatment; in those with a score of 1 («intermediate risk» of 0.6% of an embolic event per year) if it is male or 2 if it is female, they benefit more with oral anticoagulation with VKA or DOAC.[1] The HAS- BLED or ATRIA scales can be used to assess the risk of bleeding *(Table 1)*.[53]

For individuals scoring 2 or more on the CHA_2DS_2-VASc scale («high risk», 3% embolic event per year) there is no doubt that formal anticoagulation with VKA or DOAC is required. There are currently three DOACs available in Mexico: dabigatran, rivaroxaban, and apixaban. Their mechanism of action is inhibition of thrombin (dabigatran) or inhibition of factor Xa (rivaroxaban and apixaban).[54]

Each has a different dosage, which varies with the individual's age (in the case of apixaban) and kidney function (all). None can be used in cases of renal failure with creatinine clearance less than 15 mL/min. For a complete review of DOAC including dosages, how to start them, switching from VKA to DOAC, drug interactions, and bleeding management, the clinical practice guidelines of the European Heart Rhythm Association are highly recommended.[55]

V d. Left atrial appendage occluders (LAAO)

LAAO is an interventional option for the prevention of embolism that so far is only indicated for patients with high embolic risk and who have some contraindication to receive VKA or DOAC.[56]

Outside of this select group of patients, implanting these devices as substitutes for anticoagulation does not yet have sufficient evidence. The most recent results on cost-benefit analysis using dedicated statistical models (e.g. Markov's stochastic decision model) have yielded contradictory results.[57] However, several studies are ongoing and are expected to produce positive results for occluders.[58] Like any invasive procedure, its efficacy in preventing stoke should be weighed against possible complications of its implant.

VI. FINAL REMARKS

AF, in its different forms, is considered to be the most frequent tachyarrhythmia in Mexico and should be considered as a public health problem. Its treatment includes «rhythm control» with a few antiarrhythmic drugs available in Mexico for this purpose. Ventricular rate control can be achieved with drugs or some interventional procedures, included AV junction ablation with a VVIR pacemaker implant. The role of pulmonary vein isolation is undoubted for clinical relief of symptoms with many ongoing studies on the possible effect on morbi-mortality. Thromboprophylaxis is a key and integral part of the management of any patient with AF. Recently, CENETEC (National Center for the Technical Excellence in Health, Health Ministry of Mexico) published guidelines on anti-thrombotic treatment of AF.[59]

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