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Rev Invest Clin. 2023;75(4):179-86 IN-DEPTH REVIEW

Type 2 Diabetes Mellitus and Nonvalvular Atrial Fibrillation in Mexico: National Registries Raise a Red Flag

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide and is highly prevalent in Mexico, as 10.2% of the adult population harbors this condition. T2DM is usually associated with cardiovascular comorbidities, including arrhythmias. Metabolic impairment is one of the mechanisms that contribute to tissue remodeling that affects atrial structure, and concomitant, the cardiac conduction system, both could result in atrial fibrillation (AF). AF is estimated to affect more than a half million Mexicans, and its incidence is expected to keep rising. According to national registries, T2DM is present in 28.4% of Mexican patients with AF and the coexistence of both diseases is associated with a higher risk of stroke. In clinical practice, the CHA_2DS_2-VASc risk score is useful for stroke risk stratification in patients with AF to facilitate the adequate use of anticoagulation therapy. T2DM is among the items of the CHA_2DS_2-VASc score because it correlates with an intrinsic prothrombotic state. In this narrative review, we present information that highlights the need for optimal glucose control and adequate anticoagulation in subjects with T2DM and AF. (REV INVEST CLIN. 2023;75(4):179-86)

Keywords: Nonvalvular atrial fibrillation. Type 2 diabetes mellitus. Oral anticoagulation. Stroke. Mexico.

INTRODUCTION

Mexico has one of the highest prevalence of type 2 diabetes mellitus (T2DM) in the world[1]. As much as 10.2% of the total adult population suffers from this metabolic disease[2]. Since the year 2000, T2DM has been the second cause of death in Mexicans over 60 years of age, both in men and women, only behind heart disease, a condition related to T2DM[3]. T2DM is a strong cardiovascular risk factor, frequently associated with other systemic and organic comorbidities that greatly impact population health (Table 1)[4,5].

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Table 1. A list of cardiovascular pathologies and other comorbidities in patients with T2DM

Cardiovascular	**Geriatric syndromes**	**Psychiatric**
Coronary heart disease	Frailty	Depression
Heart failure	Falls	Schizophrenia
Peripheral artery disease	Disability	Delirium
Stroke		Substance abuse
Retinopathy		
Neuropathy		
Nephropathy		
Arrhythmias		
Cancer	**Musculoskeletal**	**Gastrointestinal**
Liver	Neuropathic arthropathy	Motor dysfunction (dysmotili-ty, delayed emptying or transit)
Pancreas	Adhesive capsulitis	
Endometrium	Carpal tunnel syndrome	Autonomic neuropathy
Colon	Rotator cuff tendinopathy	Bacterial overgrowth
Breast	Dupuytren's contracture	GI remodeling
Bladder	Osteoarthritis	Diarrhea
	Fractures	
Immune	**Endocrine**	**Dermatologic**
Innate immune response defects	Pancreatitis	Pruritus
Adaptive immune response defects	Low testosterone	Acanthosis Nigricans
	Decreased CRH levels	Necrobiosis Lipoidica
	Hypercortisolism	Lichen Planus
	Decreased dehydroepiandrosterone (DHEA)	Fungal and bacterial skin in-fections
	RAAS hyperactivation	

Adapted from references[49-56].

Atrial fibrillation (AF) is reported to be present in 3.8% of subjects older than 60 years. Almost half a million individuals could suffer from this arrhythmia in Mexico, and this prevalence keeps rising[6]. In older people, nonvalvular AF (NVAF) accounts for as much as 85% of AF cases in Mexico. There are some well-known risk factors for NVAF, including male sex, age, hypertension, kidney chronic disease, smoking, obesity, coronary heart disease, and T2DM[7].

The present in-depth review was performed to study the risk factors for AF and stroke, with an emphasis on the role of T2DM; to describe the particularities of NVAF treatment in patients with T2DM; and, to analyze the evidence of optimal treatment in patients with NVAF in Mexico. A bibliographic review was performed using the following databases: PubMed, Google Scholar, and ScienceDirect. Terms used were: "nonvalvular AF", "Mexico," "diabetes mellitus in Mexico," "nonvalvular AF pathophysiology," "nonvalvular AF and diabetes mellitus," "nonvalvular AF (NVAF) and diabetes mellitus treatment," "CHA_2DS_2-VASc diabetes mellitus," "nonvalvular AF stroke," "nonvalvular AF anticoagulation," and "anticoagulation in diabetes mellitus." Known registries of AF in the Mexican population were also intentionally included: "CARMEN-AF," "GLORIA AF", "REMEFA", and "REMECAR".

TYPE 2 DIABETES MELLITUS AS A RISK FACTOR FOR AF IN THE MEXICAN POPULATION

In general, diabetes increases the risk of developing AF by 35-60%. Although higher glycated hemoglobin (HbA1c) levels, and longer evolution of diabetes, are directly correlated to an increased risk of developing AF, even diabetic patients with good glycemic control are still at increased risk[8,9]. The coexistence of T2DM and AF increases the risk of stroke by almost 80% and is related to higher mortality, hospitalization rates, and thromboembolic risk[10-12].

Table 2. Frequency of comorbidities according to gender in Mexican subjects from CARMEN-AF Registry[15]

Comorbidites (%)	Total population (n = 1,423) Percentage	Male (n = 731)	Female (n = 692)	P* value
Hypertension	72.5	71.3	73.8	ns
Diabetes	28.4	31.3	25.3	0.007
Heart failure	23.6	25.3	21.8	ns
Smoking	16.4	23.9	8.5	< 0.0001
Alcoholism	9.2	17.1	0.9	< 0.0001
Nonischemic cardiomyopathy**	8.9	10.3	7.5	0.042
Coronary artery disease	7.1	9.7	4.3	< 0.0001
Obstructive sleep apnea	3.9	5.2	2.6	0.008
Peripheral artery disease	1.8	1.0	2.7	0.01

*P value was calculated by Chi-square test.
**Hypertensive, idiopathic, and restrictive.

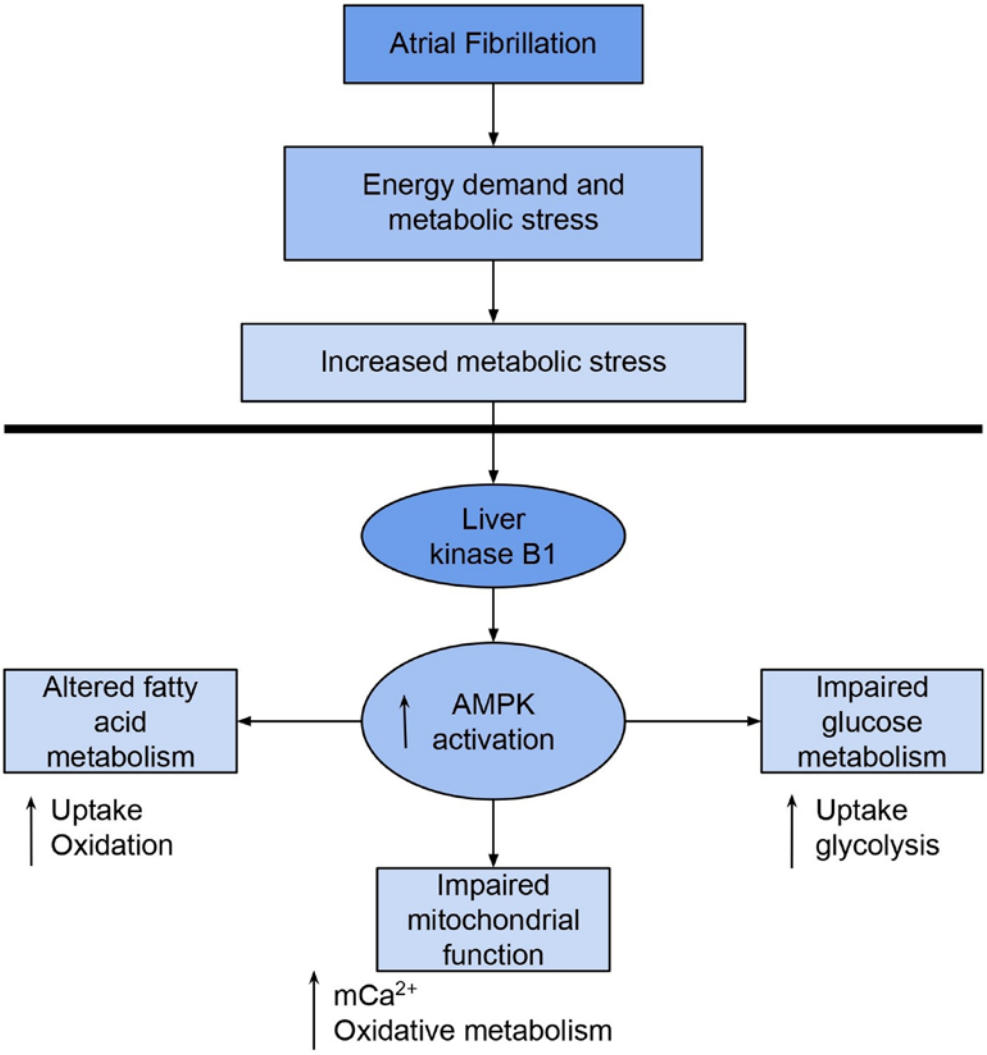
In Mexico, the Registro de Fibrilación Auricular y Riesgo Embólico en México or AF and Embolic Risk Registry (CARMEN-AF Registry) reported that the main comorbidity in Mexican patients with NVAF was hypertension (72.5%), followed by T2DM (28.4%) and heart failure (23.6%) (Table 2)[13,14]. In this Registry, paroxysmal AF was more prevalent in women (40.6%), whilst permanent AF was more prevalent in men (44%). Risk factors such as smoking, alcoholism, coronary artery disease, obstructive sleep apnea, and diabetes were more common in men[15].

We also have data from Registro Mexicano de Datos Cardiovasculares or Mexican Registry of Cardiovascular Data (REMECAR) was a descriptive-transversal study that aimed to determine the prevalence of risk factors and comorbidities present in Mexican patients with NVAF that received private medical care. Analyses of the results highlighted the association of AF, T2DM, hypothyroidism, chronic obstructive pulmonary disease (COPD), and congestive heart failure, in both men and women younger than 60 years old. AF in individuals older than 60 years old was related to chronic kidney disease and COPD. It was also noticed that men younger than 60 years are twice as likely to be diagnosed with AF when compared to women of the same age group, (1.2% and 2.4%, respectively). The incidence of AF in women increases with age, reaching as much as 33.3% in females older than 90 years of age and around 9% in men older than 70 years[16].

Multiple mechanisms could explain the linkage between T2DM and AF (Fig. 1). Glucose fluctuations induce mitochondrial respiratory chain protein dysfunction, which results in higher reactive oxygen species (ROS) levels, that are related to the progression of cardiovascular disease (Fig. 1)[17]. On the other hand, T2DM promotes electrical remodeling, which could generate reentry mechanisms necessary for the initiation of AF[18,19]. As for the progression from paroxysmal to persistent AF, modification, and expansion of epicardial adipose tissue is a source of proinflammatory mediators that induces atrial remodeling (Fig. 1)[20].

There is evidence that optimizing the management of T2DM reduces the risk of developing AF (Fig. 2). This has been attributed to the fact that some diabetes drugs exhibit anti-remodeling properties and could have direct beneficial effects on AF mechanisms. For example, metformin reduces myolysis and oxidative stress[21]. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors can reverse mitochondrial dysfunction[22]. In clinical trials, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been shown to decrease the incidence of AF[21]. Studies in animal models show that AF induction and duration are both reduced by insulin treatment. However, it is important to notice that insulin-induced hypoglycemia has been associated with higher incidences of AF[23].

Figure 2. Schematic representation of AMPK and its metabolic implications in anti-atrial arrhythmogenesis (*modified from Lkhagva et al.*[57]).



AMPK: AMP-activated protein kinase.

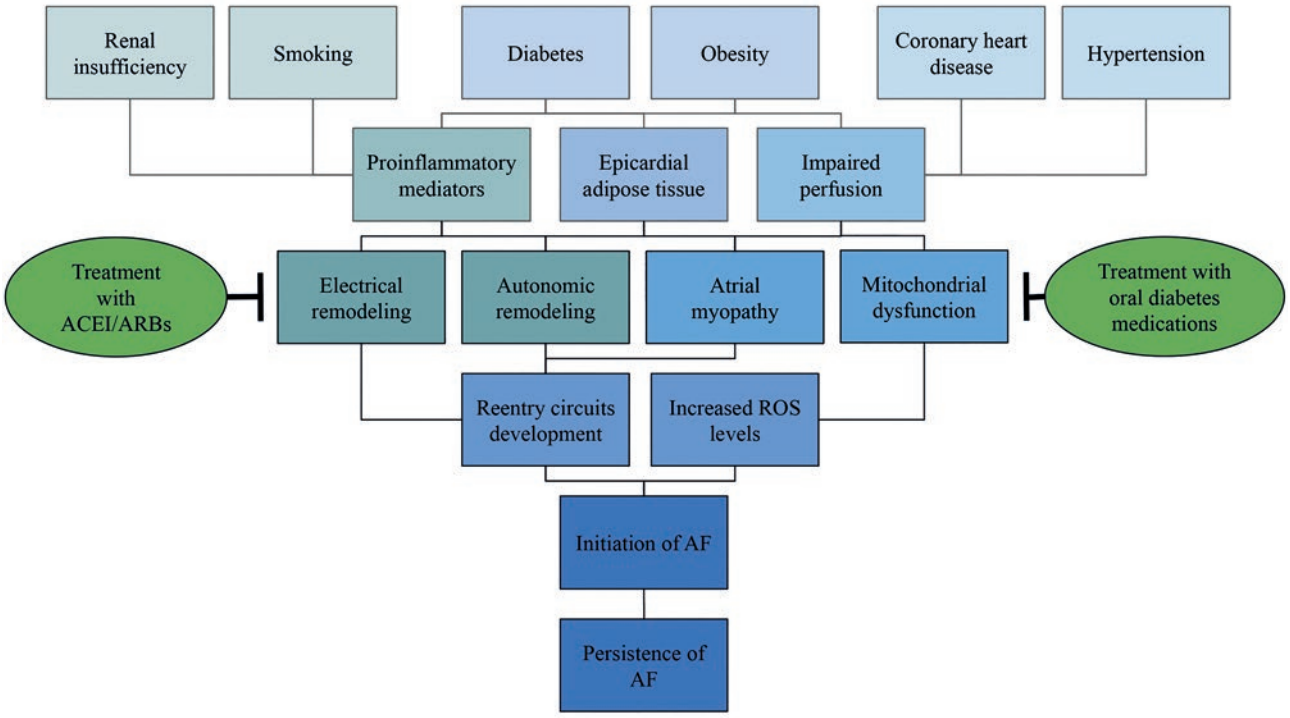
DIABETES AS A RISK FACTOR FOR STROKE IN NONVALVULAR AF

Besides promoting AF, T2DM simulates an intrinsic prothrombotic state due to platelet hyperactivity, impaired endothelial function, as well as a persistent inflammatory condition. The increased production of advanced glycation end products and ROS are known factors to trigger a hypercoagulable state in diabetic patients[24].

Diabetes is part of the CHA_2DS_2-VASc risk score, which is useful to assess stroke risk in patients with NVAF and the need for anticoagulation therapy. A combination of T2DM and age >65 years confers the highest risk for stroke compared with the other CHA_2DS_2-VASc variables[25]. Patients on insulin regimens had approximately a 2.5-fold higher risk of stroke when compared to diabetic patients that do not require insulin. This could be related to the duration of the disease and lack of adequate glucose control, rather than the use of insulin itself[26].

Atrial failure might be a late manifestation of a long-duration atrial disease that could be secondary to structural remodeling induced by T2DM which increases the risk of stroke rather than AF as an isolated entity[27]. The fact that rhythm control does not

Figure 1. Representation of pathophysiological mechanisms linking T2DM with AF.



ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin II receptor blockers.

modify the risk of stroke supports this theory[28]. T2DM is a highly consistent independent factor for stroke, because of its relation with atrial remodeling and systemic prothrombotic state. These multiple independent factors could explain why T2DM represents a robust predictor for reduced survival[29-33].

PARTICULARITIES OF NONVALVULAR ATRIAL FIBRILATION TREATMENT IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Stroke is a serious outcome of AF, so sinus rhythm maintenance is nowadays considered the best therapeutic option to reduce the risk of this complication. Although antiarrhythmic drugs have not shown promising results in patients with or without T2DM, catheter ablation seems to be an adequate approach as it provides significant clinical benefits and has been demonstrated to reduce the recurrence of AF[8,34].

Regarding treatment modalities for AF in Mexico, the Registro Mexicano de Fibrilación Auricular or Mexican Registry of AF (ReMeFa) compared the outcome of subjects with AF treated with either rhythm control or rate control. Data demonstrated that patients treated with rate control strategies were older than those managed with rhythm control, 68 ± 13 versus 64 ± 14 years old, respectively; and were more likely to be diagnosed with non-paroxysmal AF (91%), heart valve disease (42%), congestive heart failure (25%), and T2DM (25%). After a year of follow-up, stroke appeared in 3% of the rate control-managed patients and 1% of those treated with rhythm control[35].

On the other hand, concerning the anticoagulation treatment in Latin Americans with AF, the GLORIA-AF registry aimed to determine the safety and efficacy of dabigatran in patients with NVAF. Latin American population included were 44.6% female, and the average age was 69.6 years; paroxysmal AF was present in 43.8%, persistent AF in 34.7%, and 21.5% had permanent AF. The mean CHA_2DS_2-VASc was 3.2 ± 1.5 and a HAS-BLED score, a tool for bleeding risk assessment, was 1.2 ± 0.9. The final analysis showed a low rate of ischemic stroke and adverse reactions associated with anticoagulation treatment with dabigatran[36].

The analysis reported by the CARMEN-AF registry showed that 16.4% of patients were not receiving antithrombotic treatment, 19.4% had treatment with antiplatelet medication, 34.6% were receiving direct oral anticoagulants (DOACs), and 29.2% received vitamin K antagonists (VKA). Gender was not associated with treatment modalities. Notably, older age was associated with a lack of treatment and use of antiplatelet medication, and VKA use had an inverse relation with age. DOACs prescription was equal among age groups. Antithrombotic therapy selection was also influenced by the type of AF (VKA were more commonly prescribed in patients with permanent AF) and a worrying number of high-risk patients were not treated optimally[14].

VKA (acenocoumarin or warfarin) achieves adequate anticoagulation, but its unpredictable pharmacokinetics and narrow therapeutic index result in the need for constant monitoring of INR and drug–drug or drug-food interaction[37]. T2DM is associated with increased INR variations, even though there are no reports on safety concerns[38]. It is essential to point out that Latin American patients are at higher risk of presenting intracranial hemorrhage and death when treated with warfarin when compared with other populations[39]. At the same time, the former group is also less likely to achieve adequate INR control (understood as presenting inadequate INR values) and longer INR test intervals[40].

DOACs have shown excellent results as an alternative option to VKA. DOACs exhibit more predictable pharmacokinetics and anticoagulation, along with faster action on and offset, shorter plasma half-life, and a reduced need for monitoring. Many randomized trials have demonstrated that DOACs are equally effective as VKAs. Besides, studies showed that patients with T2DM on rivaroxaban (an oral factor X inhibitor) had a lower incidence of limb amputations and less need for endovascular revascularization when compared to warfarin users, without an increase in the risk of major bleeding[41,42]. Dabigatran (an oral factor IIa inhibitor) reduced the number of bleeding events associated with warfarin without an increment of ischemic events[43].

Another advantage of DOACs is their lack of interaction with anti-diabetic agents and the increased adherence due to fixed-dose regimen[44]. DOACs appear to have multiple elimination pathways, which decreases the likelihood of drug-drug interactions. Therefore, anti-diabetic medication should not be suspended if DOACs regimen is started[24,45].

It is important to mention that, both older age and kidney disease (a highly prevalent entity in diabetic patients) should be taken into consideration when starting anticoagulation therapy with DOACs. An individualized approach should be adopted after weighing the risks and benefits in these groups of patients. Modification of either the dosing regimen or the use of specific drugs must be considered in special populations to avoid the risks from overcoming the benefits[46]. The anticoagulation dose should be reduced in older adults and in patients with kidney disease. Regarding end-stage kidney disease, apixaban appears to be the preferred DOAC, although recent evidence suggests that patients with AF undergoing hemodialysis do not benefit from the use of DOACs[47,48]. Some studies report optimal treatment in < 60% of the high-risk population[49].

CONCLUSION

The increasing incidences of T2DM and AF explain the coexistence of both conditions with a higher risk for stroke in a significant number of patients. In the Mexican population the more frequent risk factors for AF are hypertension, T2DM, heart failure, and smoking, meanwhile T2DM and age >65 years confer the highest risk for stroke. Indeed, diabetes increases the risk of developing AF by 35-60%. The analysis of the CARMEN-AF registry showed that 16.4% of patients were not receiving antithrombotic treatment, 19.4% had treatment with antiplatelet medication, 34.6% were receiving DOACs, and 29.2% received VKA. Although DOACs offer a safe treatment profile in most studies, including Latin American population, a significant number of patients are not treated properly and therefore have an increased risk of stroke, which has raised a red flag, considering the high CHA_2DS_2-VASc score of this population.

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