ABSTRACT ● Recent evidence suggests that diabetic patients are at increased risk to develop arrhythmias. This brief review presents this evidence and the relationship between diabetes mellitus (DM) and arrhythmias, specifically atrial fibrillation (AF) and ventricular arrhythmias (VAs).

Animal studies have demonstrated that hyperglycemia induces oxidative stress that results in myocardial injury and cell ischemia which predispose to AF. Furthermore, prolonged hyperglycemia results in the formation of advanced glycosylation end products which invade the myocardium and lead to diabetic cardiomyopathy forming a substrate for anatomic and electrical atrial remodeling predisposing to AF as well.

Patients with DM and without known cardiovascular disease have significantly higher incidences of T-wave alternans (TWA) than non-DM patients. These TWA occurrences are positively correlated to HbA1c level. DM also produces a diabetic myocardium vulnerable to VAs and plays a crucial role in triggering these arrhythmias.

In conclusion, further randomized controlled trials are needed to verify the mechanisms that result in arrhythmias in patients with DM and which lead to major cardiovascular complications and mortality. The focus of interventions should be based on primary prevention of diabetes, coronary artery disease, and atherosclerosis until novel mechanism-based approaches that reduce arrhythmias in patients with DM are established.

Keywords: diabetes mellitus; atrial fibrillation; ventricular arrhythmias

INTRODUCTION

Diabetes is a cardiovascular risk factor that results in significant morbidity and mortality [1]. Even though coronary artery disease is the most well-established diabetic cardiovascular complication, recent evidence suggests that diabetic patients are at increased risk to develop arrhythmias [2]. Some of the mechanisms that generate arrhythmias include: autonomic imbalance, silent ischemia, inflammation, genetic predisposition, and QTc prolongation (Table I). Other mechanisms exist as well. In this brief review, the relationship between diabetes mellitus and arrhythmias, specifically atrial fibrillation and ventricular arrhythmias will be presented.
Atrial fibrillation and diabetes mellitus

Atrial fibrillation (AF) is the most common arrhythmia worldwide. With the ageing population, the prevalence of AF is going to increase by 2.5-fold in the next 50 years [3]. AF is associated with multiple complications including heart failure (HF) and thromboembolism, and it significantly increases mortality [4]. A concomitant disease in patients with AF [5], diabetes mellitus (DM) has become a major pandemic over the past few decades in the western world as well as developing countries due to over-nutrition, sedentary habits and genetic predisposition. AF and DM share common antecedents such as obesity, atherosclerosis and hypertension [6], and the causal relationship between them shall be discussed.

The Framingham Heart Study showed that AF is one of the main cardiovascular complications associated with DM. DM conferred an odds ratio of 1.4 for men and 1.6 for women, after multivariate adjustment, for developing AF [7] (Table II). In the same study, AF incidence in patients with diabetes was 14.9%; furthermore, atrial flutter occurs in 4% of diabetic patients compared with 2.5% in the control group [8]. Moreover, metabolic syndrome, which is interrelated to obesity as well as DM, is a well-established risk factor for AF [9].

Another possible pathophysiological mechanism linking obesity with DM and AF is the “lipotoxicity theory” whereby the accumulation of adipose tissue results in diabetic cardiomyopathy and myocardial lipotoxicity which in turn result in myocardial inflammation and oxidative stress that is followed by autonomic dysfunction, myocardial fibrosis and fatty infiltration which in

TABLE I ARRHYTHMIAS AND ASSOCIATED PATHOPHYSIOLOGY

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Pathophysiology</th>
<th>Studies</th>
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<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Lipotoxicity</td>
<td>Boudina et al. [10]</td>
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<td></td>
<td>Formation of AGEs</td>
<td>Morrow et al. [16], Liu et al. [20], Kato et al. [21], Igarashi et al. [22]</td>
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<td></td>
<td>Pulmonary vein ganglia remodeling</td>
<td>Bassil et al. [19]</td>
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<td></td>
<td>Genetic mutations</td>
<td>Kirchhof et al. [25], Amar et al. [26], Ellinor et al. [27], Fatini et al. [29]</td>
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<tr>
<td>Ventricular arrhythmia</td>
<td>Prolonged QTc</td>
<td>Cardoso et al. [51]</td>
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<td>T-wave alternans</td>
<td>Molon et al. [52]</td>
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<td></td>
<td>Autonomic neuropathy</td>
<td>Vinik et al. [53]</td>
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turn result in reentry (stabilized), followed by ectopic activity and hence, AF [10].

The relationship between AF and DM is that of great significance. Because of the silent progression of DM, many cases of DM remain undiagnosed until they reach an advanced stage. During this time, many DM-related complications would be progressing without treatment for quite some time. Thus, when AF occurs in this population it would carry a worse prognosis and a higher mortality rate [11]. Hence, efforts have been made to understand the altered molecular pathways in DM patients that may affect the initiation and/or progression of AF.

The mechanism of AF is still elusive. The current unified electrophysiological hypothesis of how AF initiates and perpetuates is that focal areas localized to the inside of pulmonary veins (PVs) are what trigger the initiation of reentry circuits which over time result in atrial remodeling which results in additional focal triggers that perpetuate microwave reentry [12]. Ionic currents across the cardiac myocyte which are products of the five phases of the cardiac action potential can cause arrhythmogenesis when alterations in the cardiac action potential duration (APD) occurs. Vernakalant and amiodarone are atrial peak Ina blockers that have an established therapeutic effect on the suppression of AF because of their rate-dependent reduction of excitability, prolongation of APD and hence, effective refractory period (ERP). Reduction of intracellular calcium loading via late Ina inhibition may suppress triggers that initiate AF especially in the setting of prolonged APD and bradycardia [13]. Ranolazine, a late Ina current blocker, has been shown to reduce reactive oxygen species (ROS) hydrogen peroxide-induced arrhythmogenic activity in rabbits and pigs by prolongation of the ADP due to reactive species [14]. Furthermore, in the post hoc analysis of the MERLIN-TIMI 36 trial, ranolazine which was given in patients with acute coronary syndrome led to fewer episodes of new onset AF with a lower overall AF burden [15]. Ranolazine also significantly reduced the levels of HbA1c in diabetics in the same group and reduced the incidence of increased HbA1c in patients without evidence of previous hyper-

TABLE II DIABETES MELLITUS: RISK FACTOR FOR ATRIAL FIBRILLATION

<table>
<thead>
<tr>
<th>Studies</th>
<th>Diabetes mellitus &amp; Atrial fibrillation</th>
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<tbody>
<tr>
<td>Framingham Study [7]</td>
<td>DM + AF = 1.4 in males</td>
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<tr>
<td></td>
<td>= 1.6 in females</td>
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<tr>
<td>ALFA study [26]</td>
<td>DM in chronic AF patients 13%</td>
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<tr>
<td>Manitoba study</td>
<td>Age specific incidence of AF in 4000 males</td>
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<td></td>
<td>DM + AF = Relative risk of 1.8</td>
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<tr>
<td>DM: diabetes mellitus</td>
<td>AF: atrial fibrillation</td>
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glycemia [16]. In addition, ranolazine is effective in the facilitation of restoration of sinus rhythm when added to amiodarone (especially in patients with dilated atria) [17]. The HARMONY trial has also validated ranolazine’s synergistic effect with dronedarone [18]. For these reasons, ranolazine proves to be an effective therapeutic option for AF in diabetic patients.

In their study on mice models, Bassil et al. showed that Type 1 DM causes pulmonary vein ganglia remodeling specifically hypotrophy of the cell bodies of sympathetic and parasympathetic cell bodies. The concomitant autonomic dysfunction through the decrease in sympathetic and parasympathetic function has been directly linked to the initiation of AF [19].

In humans, the mechanism by which hyperglycemia leads to the development of AF is still unknown. However, animal studies have demonstrated that hyperglycemia induces oxidative stress that results in myocardial injury and cell ischemia which predispose to AF [20]. Rabbit models demonstrated that hyperglycemia induces atrial interstitial fibrosis and atrial electrical remodeling. [16]. This electrical remodeling has been shown to be associated with advanced glycation end (AGE) products/receptor for AGE system [21] and overexpression of a gap junction protein Cx43 which predispose to AF [22]. In humans, deposition of collagen and AGE products in the myocardial extracellular matrix as well as the accumulation of intramyocellular triglycerides occur with increased myocardial stiffness which occurs in diastolic dysfunction [23,24]. Furthermore, insulin resistance is independently associated with increased atrial size, a known risk factor for the development of AF [24].

AF can also be a heritable disease [25]. Single gene mutations common in families with AF [26] as well as genetic variants of AF in the general population [27] have been identified. For example, the connexin 40 (Cx40) gene carrier has a significantly higher risk for developing AF [28].

Similarly, patients with polymorphisms involving the mink and eNOS genes are more predisposed to developing non-valvular AF [29]. These mutations affect genes which encode transcription factors regulating the electrical stability of the atrium as well as atrial remodeling (by influencing the atrial conduction velocity). Hence, they shorten cellular refractory periods and increase the automaticity of PVs foci [30]. An example of this is the transcription factor nuclear factor-kappa B (NF-KB). NF-KB promotes reentry by enhancing conduction heterogeneity, by affecting redox signaling pathway or angiotensin cascade [31]. In DM, hyperglycemia causes an overproduction of ROS which leads to NF-KB upregulation which promotes the transcription of pro-inflammatory genes hence promoting an inflammatory state [32].

Because of the role of NF-KB in mediating an inflammatory state in DM and the genesis of AF, therapy targeting NF-KB to suppress AF in diabetic patients is very appealing. However, currently no clinical studies are available to confirm this hypothesis.

Similarly, the transcription factor peroxisome proliferator-activated receptor gamma (PPAR-gamma) has been proven to have anti-inflammatory and anti-oxidant effects [33]. Furthermore, in elderly patients with AF, there is a strong correlation between lower levels of PPAR-gamma receptor protein and higher serum levels of inflammatory markers such as hs-CRP, IL-6 and TNF-alfa [34]. Thiazolidinediones (TZDs), in addition to their anti-diabetic activity, are PPAR-gamma activators which have been found to independently protect diabetic patients from the development of AF by Chao and colleagues after adjustment for other variables [35]. Moreover, TZDs may delay the progression of persistent AF to permanent AF in diabetic patients by affecting atrial remodeling via their effect of reducing circulating levels of pro-collagen type I carboxy terminal peptide (PICP) and advanced glycosylation end products (AGEs) [36]. Thus, further randomized controlled trials aimed to confirm these therapeutic effects of TZDs in patients with DM and AF are needed.

Prolonged hyperglycemia results in the formation of AGEs which invade the myocardium and lead to interstitial fibrosis, hypertrophy and eventually diabetic cardiomyopathy which results in a substrate for anatomic and electrical atrial remodeling [10]. Thus, the interstitial fibrosis that forms this substrate is what promotes anisotropic impulse propagation which accounts for the initiation and perpetuation of microwave reentry which begets AF. A positive linear correlation between HbA1c and risk of AF in patients with and without DM is well established [37]. However, as per the ACCORD cohort, intensive glycemic control does not affect the rate of new-onset AF [38]. In fact, patients with DM and AF had an increased risk of morbidity and mortality compared to those without AF. On the other hand, Pathak et al. highlighted the role of lifestyle modifications in the treatment as well as prevention of AF. They proved that long-term sustained weight loss (including avoidance of weight fluctuation) is associated with significant reduction of AF burden and maintenance of sinus rhythm in patients with BMI > 27 kg/m², and that a weight reduction of more than ten percent resulted in more than 6-fold of arrhythmia free survival compared to other less strict weight loss measurements (95% CI: 3.4-10.3, p < 0.001) [39]. Hence, targeting weight loss should be the first line therapy in DM obese patients with AF referred for AF therapy. This importance of aggressive risk factor modification and its effect on AF maintenance has also been
described in the ARREST-AF trial which showed in DM patients with AF who underwent AF catheter ablation, the odds of arrhythmia free survival increased 5-fold after aggressive risk factor modification [40].

The risk for ischemic stroke and hence worse outcome has been proven to be increased in patients with DM [41]. A main factor that triggers ischemic stroke in patients with DM is the occurrence of AF [42]. Patients with AF and DM have exaggerated endothelial dysfunction than patients without DM and this explains why this population might be at higher risk of developing strokes [43]. Vitamin K antagonists, for decades, have been the cornerstone for treatment of patients who are at high risk for thromboembolic disease. However, it has been shown that DM is one of the clinical factors that affects anticoagulation control during warfarin therapy. This has been demonstrated by the S.AMe-TT:R2 score [44]. Hence, warfarin therapy might not be the best treatment option in diabetic patients with AF.

Furthermore, trials comparing novel anticoagulants to warfarin (namely: RE-LY [45], ROCKE-T-AF [46], ARISTOTLE [47], and ENGAGE-AF [48]) well represented patients with DM and outcomes were comparable to those without DM. These trials proved that the relative efficacy and safety of the new anticoagulants was similar in patients with DM compared to patients without DM. Hence, it is reasonable to consider one of the new anticoagulants as first line therapy to prevent thromboembolic events in patients with DM and AF.

### Ventricular arrhythmias and diabetes mellitus

The leading cause of death in patients with DM is cardiovascular disease. DM enhances atherosclerosis and coronary artery disease, and this high incidence and extent of coronary atherosclerosis inevitably results in ventricular arrhythmias (VAs) and sudden cardiac death (SCD) [49] (Table III). The presence of other noncoronary atherosclerotic factors also play a role in strengthening the interrelation between DM, VAs and SCD. These factors include: autonomic neuropathy, microvascular disease, and ventricular electrical and structural changes [50].

Several recent studies have proven that patients with DM have prolonged QTc intervals compared to patients without DM which places these patients at a high risk for VAs [51]. Microvolt T wave alternans (TWA), another strong predictor of VAs, has also been studied in patients with DM [52]. Patients with DM and without known CVD, had significantly higher incidences of TWAs than non-DM patients; furthermore, these TWA occurrences positively correlated to the HbA1c level. For every 1% rise in HbA1c, there was a 13-fold increase in the risk of having atypical TWAs which resulted in a higher risk of spontaneous VAs. This was independent of the QTc interval duration. These trials conclude that the diabetic myocardium is electrically unstable creating potential substrates for reentry and hence VAs. This substrate is different from that of ischemic cardiomyopathy in which the substrate is scar tissue resultant from ischemia. Furthermore, autonomic neuropathy also renders this diabetic myocardium electrically unstable by perpetuating unbalanced sympathetic stimulation which predisposes to VAs [53]. In addition, cardiac sensory neuropathy predisposes to VAs and SCD via silent ischemia [54].

Not only does DM produce a diabetic myocardium vulnerable to VAs, it seems to play a crucial role in triggering these arrhythmias as well. Chen-Scarabelli and colleagues showed that suboptimal glycemic control and persistent hyperglycemia are associated with a higher risk of developing VAs [55].

### CONCLUSION:

The pathophysiological and electrophysiological mechanisms (Table I) that result in arrhythmias in patients with DM lead to major cardiovascular complications as well as mortality. Further randomized controlled trials are needed to verify these mechanisms further. We still lack a detailed comprehension of the molecular cues linking hyperglycemia, insulin resistance with arrhythmogenic substrates. Until then, the focus of interventions should be based on primary prevention of diabetes, coronary artery disease, and atherosclerosis until novel mechanism-based approaches to reduce arrhythmias in patients with DM are established.

### TABLE III

<table>
<thead>
<tr>
<th>Studies</th>
<th>Diabetic mellitus &amp; Sudden cardiac death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Study</td>
<td>DM increases risk of SCD in all age groups</td>
</tr>
<tr>
<td></td>
<td>SCD is higher in DM women &gt; Men</td>
</tr>
<tr>
<td>Nurse Health Study</td>
<td>DM 3x risk of SCD (HTN 2.5, obesity 1.6)</td>
</tr>
<tr>
<td>Honolulu Heart Program</td>
<td>DM &amp; MI increase RR of SCD than non DM</td>
</tr>
<tr>
<td>Paris Prospective Study</td>
<td>DM is a strong risk factor for SCD in the French population</td>
</tr>
</tbody>
</table>

**DM:** diabetic mellitus  
**SCD:** sudden cardiac death  
**HTN:** hypertension  
**MI:** myocardial infarction  
**RR:** relative risk

### REFERENCES


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