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WORD COUNT	1426	TIME SUBMITTED	09-MAR-2022 07:29PM
		PAPER ID	83449121

Name of Journal: *World Journal of Cardiology*
Manuscript NO: 73160
Manuscript Type: LETTER TO THE EDITOR

Glucose lowering does not necessarily reduce cardiovascular risk in type 2 diabetes

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Abstract

Diabetes mellitus (DM) is a health condition characterized by glucose dysregulation and affects millions of people worldwide. The presentation of heart failure in diabetic cardiomyopathy extends over a wide phenotypic spectrum, commencing from asymptomatic, subclinical structural abnormalities to severely symptomatic biventricular dysfunction with increased mortality risk. Similarly, the spectrum of systolic dysfunction in diabetic-induced heart failure is diverse. DM leads also to cardiac electrical remodeling reacting on various targets. Dipeptidyl peptidase-4 (DPP-4) inhibitors reduce glucagon and blood glucose levels by raising levels of the endogenous hormones glucagon-like-peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and constitute a safe and effective glucose lowering treatment option in patients with type 2 DM (T2DM). Despite DPP-4 inhibitors' efficacy regarding glycemic control, their effect on cardiovascular outcomes (myocardial infarction, stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization and cardiovascular death) in diabetic patients, has been neutral. The potential correlation between atrial flutter and DPP-4 inhibitors administration needs further investigation.

Key Words: Dipeptidyl peptidase-4 (DPP-4) inhibitors; Diabetes mellitus; Outcomes; Meta-analysis; Heart failure; Atrial flutter

Bourazana A, Giamouzis G, Skoularigis J, Triposkiadis F, Xanthopoulos A. Glucose lowering does not necessarily reduce cardiovascular risk in type 2 diabetes. *World J Cardiol* 2022; In press

Core Tip: Dipeptidyl peptidase-4 (DPP-4) inhibitors is a safe and effective glucose lowering treatment option in patients with type 2 diabetes mellitus (DM). However, their effect on cardiovascular outcomes in diabetic patients has been neutral. The potential correlation between atrial flutter and DPP-4 inhibitors administration is an interesting finding but since currently there is no sheer underlying pathophysiologic mechanism to justify it, more evidence is required.

TO THE EDITOR

Diabetes mellitus (DM) is a health condition characterized by glucose dysregulation and affects 237.9 million males and 222 million females worldwide[1]. It is an established risk factor of cardiovascular disease, atrial and ventricular arrhythmias as well as sudden cardiac death[2,3]. Dipeptidyl peptidase-4 (DPP-4) inhibitors is a safe and effective glucose lowering treatment option in patients with type 2 DM (T2DM). Nevertheless, pooled recent data on the effect of DPP-4 inhibitors on cardiovascular outcomes and major cardiac arrhythmias are lacking.

We read with great interest the paper by Patoulias *et al*[4], who attempted to close the abovementioned knowledge gap by performing a meta-analysis of 6 randomized controlled trials (52520 patients) concerning the impact of dipeptidyl peptidase-4 (DPP-4) inhibitors on "hard" cardiovascular outcomes and major cardiac arrhythmias. The authors concluded that DPP-4 inhibitors, compared to placebo, had no effect on fatal or non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization and cardiovascular death and did not seem to confer any significant risk for major cardiac arrhythmias, with the exception of atrial flutter, which was associated with an increased risk equal to 52% (RR = 1.52, 95% CI: 1.03-2.24, I^2 = 0%).

We agree with the authors' insight that the presence of DM per se increases the risk of adverse cardiovascular outcomes and arrhythmias and results in cellular destabilization of myocardial tissue altogether. For example, it has been demonstrated that diabetic patients present an increased propensity for developing heart failure[5]. Diabetic cardiomyopathy, defined as ventricular dysfunction in the absence of hypertension or coronary artery disease, has been attributed to the deregulated immune response in type-1 DM (T1DM) and to the background of obesity in the majority of T2DM patients. The amplified immune response of T1DM patients objects cardiac antigens such as MYH6 and a-myosin segments that have been exposed to vascular surface after the chronic, low grade hyperglycemia-mediated inflammation of cardiac tissue. On the other hand, obesity that predominates over T2DM patients reduces the palliative

actions of circulating natriuretic peptides on ventricular stress, pressure overload and sympathetic activation. In the absence of natriuretic peptides' favorable actions, left ventricle hypertrophy, fibrosis and insulin desensitization in skeletal muscles are more frequently observed in obese patients[5]. The presentation of heart failure in diabetic cardiomyopathy extends over a wide phenotypic spectrum, commencing from asymptomatic, subclinical structural abnormalities, developing progressively to severely symptomatic biventricular dysfunction with advanced mortality risk. Similarly, the spectrum of systolic dysfunction in diabetic-induced heart failure is diverse, originating in the heterogeneous risk factors that diabetes comes along, such as hypertension, hyperlipidemia, cardiovascular disease, and chronic kidney disease[6].

Except for the morphological implications on ventricular myocardium which account for the wide spectrum of left ventricular dysfunction, DM leads to cardiac electrical remodeling reacting on various targets. Among the diabetes-induced electrical disturbances, reduced conduction velocity, prolonged repolarization, and increased QT dispersion have been recognized, all predisposing to ventricular arrhythmias[7,8]. T1DM and T2DM leads to action potential duration prolongation which becomes prominent on electrocardiography (ECG) with a QRS prolongation in some diabetic patients[9]. QT duration prolongation subsequently predisposes to early after depolarizations development and an enhanced risk of torsade de pointes[10]. The proposed mechanisms are diabetes-exerted alterations in the function of several proteins involved in ion handling. More specifically DM modifies ion channels responsible for depolarization, as well as repolarization and resting phase[11]. Therefore, DM affects essentially all phases of action potential and correlates strongly to ventricular arrhythmias emergence.

The culprit pathophysiological mechanisms for the occurrence of atrial arrhythmias in DM substrate are not yet in depth elucidated. In atrial myocardium DM favors the phenotypic switch of fyobroblasts to myofriblasts[12]. Mighty it is that diabetes induced atrial neuropathy as well as diabetes generated advanced myofibroblast differentiation promote atrial remodeling and lead to atrial cardiomyopathy overall[13]. Nonetheless,

on epidemiological basis, DM is a strong independent risk factor for atrial fibrillation and atrial flutter occurrence.

Several studies have demonstrated that antidiabetic drugs may have differing effects on the risk of new-onset atrial fibrillation (AF)[14]. Metformin has been associated with anti-atrial arrhythmic benefits[15]. A case control study revealed no association between sulfonylurea and incident AF, whereas the use of insulin was associated with increased risk of new-onset AF[16]. A recent meta-analysis showed that DPP-4 inhibitor treatment resulted in a non-significant decrease in the risk for AF, whereas both glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2-i) were associated with a significant decrease in the risk for AF, equal to 14% and 19%, respectively[17]. Liraglutide (a GLP-1RA) demonstrated favorable effects on electrophysiological changes regarding AF inducibility and conduction velocity decrease [18].

DPP-4 inhibitors reduce glucagon and blood glucose levels by raising levels of the endogenous hormones glucagon-like-peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) which are called incretins. Subsequently incretins inhibit glucagon release and increase insulin secretion. Despite DPP-4 inhibitors' indisputable efficacy regarding glycemic control, their effect on cardiovascular outcomes in diabetic patients, as denoted in the aforementioned and previous studies, has been neutral[19,20]. Furthermore, the risk of hypoglycemia is admitted to be increased compared to SGLT-2i. SGLT-2i reduce hyperglycemia through inhibition of glucose reabsorption in the renal proximal tubules. Acting on glucose/Na co-transporter they promote natriuresis and display not solely hypoglycemic effects but also reduce major adverse cardiovascular events (cardiovascular and total mortality, fatal or nonfatal myocardial infarction or stroke), hospitalization for heart failure and improve outcome in chronic kidney disease in diabetic and non-diabetic patients[21]. GLP1-RA are oral hypoglycemic drugs which mimic the effects of the incretin hormone GLP-1. GLP-RA stimulate insulin release, inhibit glucagon secretion, and slow gastric emptying. Liraglutide, albiglutide, dualiglutide have all shown significant decreases in adverse cardiovascular events[22]. In

line with this evidence, the European Society of Cardiology (ESC) guidelines recommend the administration of SGLT-2i or GLP1-RA as a first option in the presence of high or remarkably high cardiovascular risk or of cardiovascular disease[23].

The potential correlation between atrial flutter and DPP-4 inhibitors administration is an interesting finding but since there is no sheer underlying pathophysiologic mechanism to justify it, more evidence is required to establish this thesis as a widely accepted knowledge, admissible in clinical practice. The authors speculated that the abovementioned correlation may stem from the inherent higher risk of atrial flutter that patients with DM carry[24]. However, it is also well known that DM per se is a risk factor of atrial fibrillation[24] which in the current meta-analysis was not associated with DPP-4 inhibitors use.

In conclusion, the authors should be congratulated on their attempt to provide state of the art data on the association between DPP-4 inhibitors and cardiovascular outcomes as well as major cardiac arrhythmias. The reported increased risk of atrial flutter in patients receiving DPP-4 inhibitors needs further investigation (Figure 1).

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