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**EDITORIAL**

Cheng CH, Hao WR, Cheng TH. Unveiling mitochondrial mysteries: Exploring novel tRNA variants in type 2 diabetes mellitus. *World J Diabetes* 2025; 16(1): 98798 [DOI: [10.4239/wjd.v16.i1.98798](https://doi.org/10.4239/wjd.v16.i1.98798)]

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**MINIREVIEWS**

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**ORIGINAL ARTICLE****Retrospective Study**

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**Clinical Trials Study**

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**Prospective Study**

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**SYSTEMATIC REVIEWS**

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**SCIENTOMETRICS**

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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJD* mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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## Prediabetes and atrial fibrillation risk stratification, phenotyping, and possible reversal to normoglycemia

Hyder O Mirghani

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### Abstract

Patients admitted with prediabetes and atrial fibrillation are at high risk for major adverse cardiac or cerebrovascular events independent of confounding variables. The shared pathophysiology between these three serious but common diseases and their association with atherosclerotic cardiovascular risk factors establish a vicious circle culminating in high atherogenicity. Because of that, it is of paramount importance to perform risk stratification of patients with prediabetes to define phenotypes that benefit from various interventions. Furthermore, stress hyperglycemia assessment of hospitalized patients and consensus on the definition of prediabetes is vital. The roles lifestyle and metformin play in prediabetes are well established. However, the role of glucagon-like peptide agonists and metabolic surgery is less clear. Prediabetes is considered an intermediate between normoglycemia and diabetes along the blood glucose continuum. One billion people are expected to suffer from prediabetes by the year 2045. Therefore, real-world randomized controlled trials to assess major adverse cardiac or cerebrovascular event risk reduction and reversal/prevention of type 2 diabetes among patients are needed to determine the proper interventions.

**Key Words:** Major adverse cardiac or cerebrovascular event; Prediabetes; Risk stratification; Phenotype; Stress hyperglycemia; Reversal to normoglycemia

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**Core Tip:** Patients admitted with prediabetes and atrial fibrillation are at high risk of major adverse cardiac or cerebrovascular events independent of confounding variables, as shown by Desai *et al.* The shared pathophysiology between the three serious and common diseases establish a vicious circle, culminating in high atherogenicity. In another study, Batta and Hatwal raised important points regarding risk stratification, timeline the role of metformin use among patients with prediabetes, and the impact of reversion of prediabetes to normoglycemia on major adverse cardiac or cerebrovascular events. We congratulate Desai *et al* for their valuable results and Batta and Hatwal for their insights and future directions. We believe and support the above. However, the studies approached inpatients retrospectively. Another important issue that can influence diabetes outcomes is stress hyperglycemia. Here, we give broader insight into proper interventions to reduce the risk of major adverse cardiac or cerebrovascular events in particular glucagon-like peptide-1 agonists, sodium-glucose cotransporters-2 inhibitors, and bariatric surgery.

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## INTRODUCTION

Prediabetes, major adverse cardiac or cerebrovascular events (MACCE), and atrial fibrillation are common and serious diseases. When they co-exist, they exacerbate each other and initiate a vicious cycle with serious consequences. The shared pathophysiology and the interaction of the above diseases with cardiovascular risk factors substantially impact the patient's outcomes. Literature on this important health problem is scarce. Desai *et al*[1] touched on this critically important issue and published the largest retrospective study to date. The authors assessed the influence of prediabetes on MACCE among inpatients with atrial fibrillation and found that prediabetes is an independent risk factor for MACCE. However, the authors assessed only hospitalized patients, and the sample population was elderly with high cardiovascular risk factors, atherosclerotic cardiovascular disease, and hyperthyroidism. Furthermore, the diagnostic test for prediabetes and the duration of diabetes was not mentioned. Although it is difficult to draw a cause and effect, the above results imply that this sample of high cardiovascular-risk patients might not have received the right management to reduce/prevent them from admission with heart failure. Novel antidiabetic medications with cardiorenal benefits like glucagon-like peptide-1 receptor agonists and some sodium-glucose cotransporters-2 inhibitors are approved for hospitalized patients with heart failure and MACCE[2].

Importantly, the retrospective nature of the study did not allow for the categorization of patients into newly discovered diabetes or known cases of diabetes. In addition, prediabetes might be confused with stress hyperglycemia, another important problem with similar pathophysiology and negative influence on the patient's outcomes[3,4]. Stress hyperglycemia is the admission of blood glucose  $\geq 140$  mg/dL after ruling out type 2 diabetes, although this is above the range of impaired fasting glucose[5]. However, the range fits impaired glucose tolerance, and some atrial fibrillation patients could present with both prediabetes and stress hyperglycemia. Hyperglycemia ratio (admission hyperglycemia/average blood glucose derived from the glycated hemoglobin) is a novel biomarker of hyperglycemia in critically ill patients, including those with MACCE. It was shown to be associated with poor outcomes and a risk factor for cardiovascular disease[6,7]. An interesting and important issue raised by Batta and Hatwal[8] is the risk quantification of MACCE across different glucose profiles, the role of metformin, and the reversal of prediabetes to normoglycemia. The authors touched on an important issue with significant clinical implications because 50% of the United States population  $> 65$  years have prediabetes[9], which is a risk factor for atrial fibrillation and MACCE. Several attempts for risk stratification of prediabetes were developed, including the Institute for Health and Care Excellence Risk Score, the American diabetes risk score, and the metabolic syndrome clusters. Risk stratification is vital for individualization of intervention and even precision medicine for different prediabetes phenotypes[10]. Dividing prediabetes into phenotypes helps predict which complication could develop, as metabolic syndrome variants are more likely to develop renal problems and insulin deficiency is linked to retinopathy[11]. Depending on the phenotype and cardiac risk factors, some patients with prediabetes could benefit from liraglutide[12], semaglutide[13], or bariatric/metabolic surgery[14].

## DIFFERENTIATION OF PREDIABETES AND DIABETES FROM STRESS HYPERGLYCEMIA

Stress hyperglycemia is a transient state of high blood glucose due to underlying illness[15]. Stress hyperglycemia is defined as a fasting blood glucose of  $> 6.9$  mmol/L, and random blood glucose  $> 11.1$  mmol/L that reverses to normal after hospital discharge. At the same time, known diabetes mellitus is the diagnosis of diabetes before hospital admission, fasting blood glucose of  $> 6.9$  mmol/L, random blood glucose  $> 11.1$  mmol/L during the hospital stay, and confirmed after discharge[16,17]. Stress hyperglycemia is common in hospitalized patients and is a predictor of future diabetes mellitus[18]. The introduction of glycated hemoglobin to diagnose diabetes significantly helps differentiate stress hyperglycemia from diabetes and prediabetes[19]. However, a single glycated hemoglobin (HbA1c) is unreliable, and

**Table 1** Diagnosis of stress hyperglycemia, prediabetes, and diabetes mellitus

Character	Stress hyperglycemia	Prediabetes	Diabetes
History	No history of diabetes or prediabetes	No history of diabetes	Known case of diabetes or confirmed by diabetes based on blood glucose and HbA1c
Blood tests	Fasting blood glucose of > 6.9 mmol/L, random blood glucose > 11.1 mmol/L that reverse to normal after hospital discharge	Fasting blood glucose: 5.6-6.9 mmol/L, 2 hours after a 75 g oral glucose tolerance: 7.8-11.1 mmol/L, and HbA1c: 5.8-6.4	Fasting blood glucose of > 6.9 mmol/L, random blood glucose > 11.1 mmol/L during hospital stay and confirmed after discharge, and HbA1c $\geq$ 6.5

HbA1c: Glycated hemoglobin.

repeat testing is required[20]. Importantly prediabetes could be a risk factor for stress hyperglycemia; therefore, combining both blood glucose and HbA1c is vital to differentiate between the two conditions in the hospital setting[21] (Table 1).

In addition to the importance of metformin use raised by Batta and Hatwal[8] is lifestyle modification, which was shown to reduce mortality among patients with prediabetes who reverse to normoglycemia in contrast to their counterparts who were physically inactive or have obesity[22]. The association of reversal to normoglycemia from prediabetes and mortality is a matter of debate with some studies showing reduction[23,24] and others showing no association[25]. A plausible explanation of the above contradiction could be the population, sample size, and the associated cardiovascular risk factors including smoking, obesity, and sedentary lifestyle[26]. Because prediabetes is considered an intermediate between normoglycemia and diabetes and one billion people are expected to suffer from prediabetes by the year 2045 [27], risk stratification, phenotyping, and consensus on prediabetes cut-off values are essential for proper intervention.

The limitation of the original research is that it is retrospective and included only elderly hospitalized patients who were at high-risk of cardiovascular disease.

## CONCLUSION

Patients admitted with prediabetes and atrial fibrillation are at high risk of MACCE, independent of confounding variables, due to shared pathophysiology between the three serious/common diseases and their association with atherosclerotic cardiovascular risk factors. Risk stratification of patients with prediabetes to define phenotypes that benefit from various interventions including glucagon-like peptide-1 receptor agonists and bariatric surgery is of paramount importance, and stress hyperglycemia assessment among hospitalized patients is vital. Prediabetes is considered an intermediate between normoglycemia and diabetes and one billion people are expected to suffer from prediabetes by the year 2045. Therefore, real-world randomized controlled trials to assess MACCE risk reduction and reversal/prevention of type 2 diabetes to reflect the real state of the problem and direct the proper interventions are necessary.

## FOOTNOTES

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