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A Review on Assessment of Cardiovascular Risk in Type II Diabetes Patients by Using Mr-proANP and NT-proBNP

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Abstract

Aim: Cardiovascular disease is mainly affected to the patients with type 2 diabetes and the person with diabetic condition more prone to CVD than the person with non-diabetic condition. T2DM and CVD are correlated with each other with the condition of prolong lifestyle with improper diet and medication.

Methodology: Moreover, the T2DM with no existence CVD are predicted to develop the CVD with high mortality rate than the non-diabetic patients. So that developing the biomarker in the prediabetic condition will helps to identify the HF event. Emerging research are involved in the identification of the biomarkers which may helpful to predict the CVD in diabetes patients.

Results: At present, the more focus is turned towards the natriuretic peptides which can used to detect the CVD events in diabetes patients. Measurement of the BNP and ANP natriuretic peptides in the circulating bloods are recently used for diagnostic and prognostic of CVD. ANP are mostly used as an alternative for BNP in predicting heart failure, which was only observed with minor difference.

Conclusion: This review deals with the information on the wide role of MR-proANP and NT-proBNP as the potential diagnostic and prognostic in cardiovascular risk with T2DM.

Keywords: Heart failure; Cardiovascular disease; Diabetes; Natriuretic peptide

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Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the major disease conditions which leads to Cardiovascular Disease (CVD). Recent years, T2DM with cardiovascular disease has surpassed cancer as the leading cause of morbidity and mortality worldwide [1]. In people with T2DM, CVD act as the major factor for mortality. To reduce the macrovascular complications of diabetes, it is critical to manage CVD risk factors such as high blood glucose, blood pressure, imbalance of lipid level, obesity, cigarette smoking, and lack of physical activity [2]. Several studies have found that patients with diabetic condition are more prone to develop and dying from CVD than the patients have metabolism with no diabetes [3]. The CVD was reported to cause 68% of mortality rate in diabetes related patients in the United States in 2004, and stroke was mentioned on 16% [2]. Despite the fact that preventive strategies for controlling the CVD in diabetes patients was not completely inadequate. It was also reported that patients with prediabetic condition have the ability easily recovered from the CVD risk. While after the development of diabetic condition it required a periodic treatment [4].

Emerging field of research was going on Natriuretic Peptides (NPs) as a biomarker for monitoring the health of diabetic patients with CVD [5]. Recently, NPs was used as a key regulator in maintaining the normal metabolism and their level in the diabetes patients are used for changing the treatment paradigm [6]. The importance of NPs in maintaining cardiovascular homeostasis has been well established in recent decades [7], but their benefits in CVD and diabetes are further needed to be explored more [8]. The cardiac circulating hormone NPs play a significant role in intravascular blood volume and regulate the energy usage and metabolism of endocrine organs. These NPs can help as to identify the new strategic way of preventing the T2DM and obesity [6,9]. The peptide which are inactive has the high half-life of plasma and these peptides can be processed to active peptides. The human NP gene encoded equimolar concentration of inactive fragments

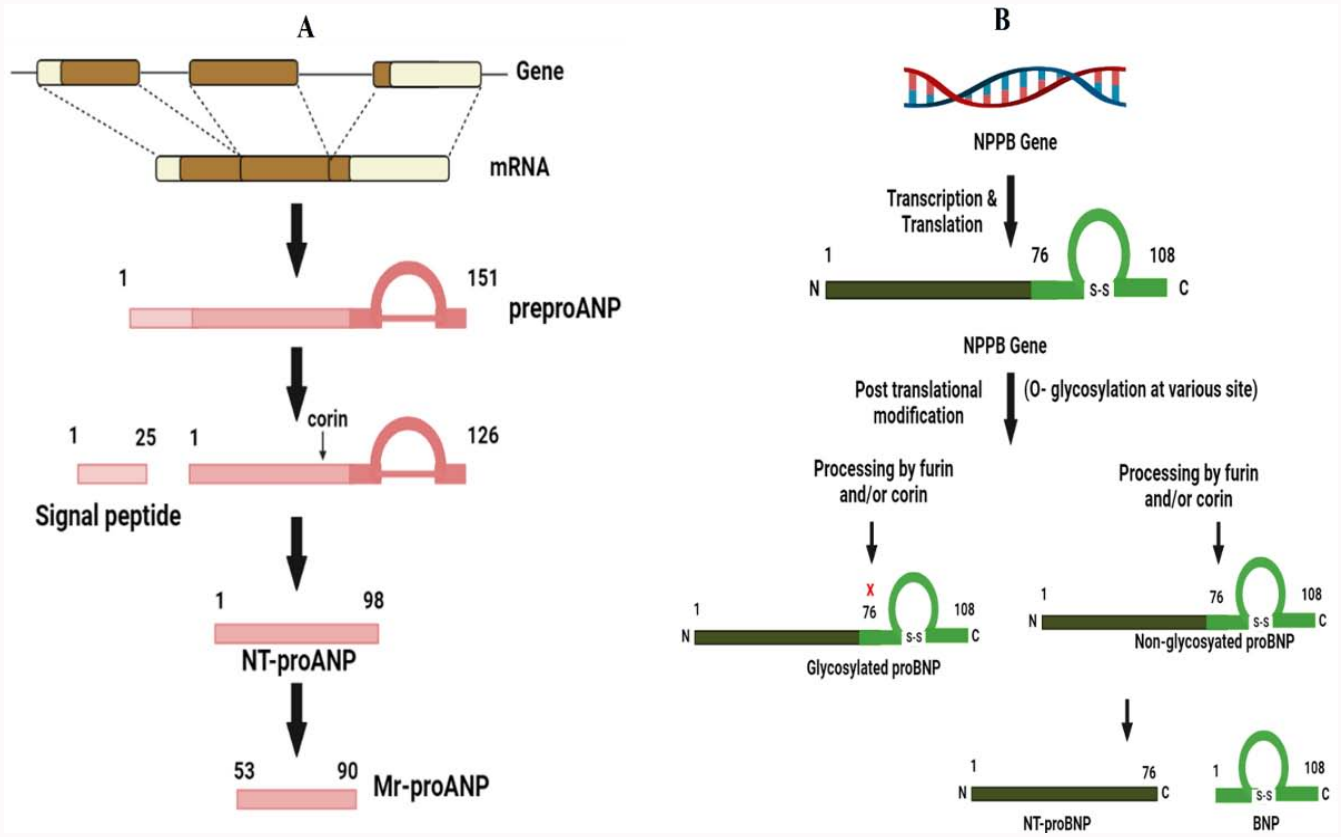

Figure 1: Gene expression, translation, and processing of Mr-proANP and NT-proBNP are represented schematically. (A) In the degradation of NT-proANP, the fragment of MR-proANP is identified in human plasma. (B) In the degradation of non-glycosylated proBNP, the fragment of NT-proBNP is identified.

of peptide used as a biomarker for various clinical propose [10]. The NPs includes N-Terminal B-type Natriuretic Peptides (NT-proBNP) and Midregional proA type Natriuretic Peptide (MR-proANP). The Corin enzymes are involved in producing active ANP from proANP. The proBNP are cleaved by Corin and furin to active BNP and inactive fragment NT-proBNP in the N-terminal region frequently for post-translationally O-glycosylation. Mr-proANP and NT-proBNP are used as a biomarker for diagnostic and prognostic of HF both the diabetes and non-diabetes patients [11,12]. The interest in biomarkers of HF and diabetes are growing widely since the Mr-proANP and NT-proBNP provide a quantitative information about the CVD and its complication related diabetes. This review deals with the information on the wide role of MR-proANP and NT-proBNP as the potential diagnostic and prognostic in cardiovascular risk with T2DM.

Mr-proANP and NT-proBNP Natriuretic Peptide

A high level of natriuretic peptide is a sensitive marker of hemodynamic status for the indication of an unstable heart state, i.e., a maladaptive cardiac remodeling that leads to a cardiovascular event [13]. However, only BNP and NT-proBNP are used to diagnose Heart Failure (HF), and there is no data on MR-proANP [14]. Similarly, to B-type natriuretic peptides, ANP could be used as a prognostic for HFpEF. In obese patients with HF, ANP has been shown to improve the diagnostic performance of BNP [15]. ANP, on the other hand, accounts for the majority to 98% of all circulating NPs. Because proANP, the precursor of ANP, is significantly more stable in circulation than the mature peptide, it may be used to overcome the reproducibility issue [16]. MR-proANP is a new myocardial stretch biomarker that can aid in the identification and prognosis of patients with metabolic disease who have HF [17]. The ANP gene (NPPA), which has three exons and two introns, produces ANP mRNA. The coding and non-coding regions are indicated by brown and yellow boxes, respectively. ANP is made from pre-proANP, a preprohormone that is cleaved from a signal peptide to produce proANP, an ANP precursor. This precursor is converted by Corin into bioactive ANP and NT-proANP. ANP is also synthesized in pathophysiological conditions by an unidentified mechanism. In the degradation of NT-proANP, the fragment of MR-proANP is identified in human plasma (Figure 1A). The NPPB early-response gene produces BNP. Its blood levels peak one hour after stimulation and are primarily produced *de novo* by the ventricular myocardium in response to mechanical, hormonal, or sympathetic stimulation [18]. Transpulmonary pressure in the lungs, oxygen demand, or pro-inflammatory factors all stimulate NPPB transcription, resulting in 134-amino acid pre-proBNP. In the sarcoplasmic reticulum, a signal peptide is then removed, leaving 108-aa proBNP. When secreted into the bloodstream, the two biomarkers such as BNP (32 amino acid) and NT-proBNP (76-amino acid) [19].

In the diagnosis of HF, MR-proANP is recommended for patients with BNP and NT-proBNP values in the "grey zone," as well as obese patients. The use of MR-proANP in combination with BNP and NT-proBNP can improve diagnosis accuracy, but it can also reduce specificity [20]. MR-proANP is an independent predictor of poor prognosis in patients with HF, and some studies have even found that it is more accurate than NT-proBNP [21,22]. In patients, MR-proANP was effective as NT-proBNP in predicting mortality. After

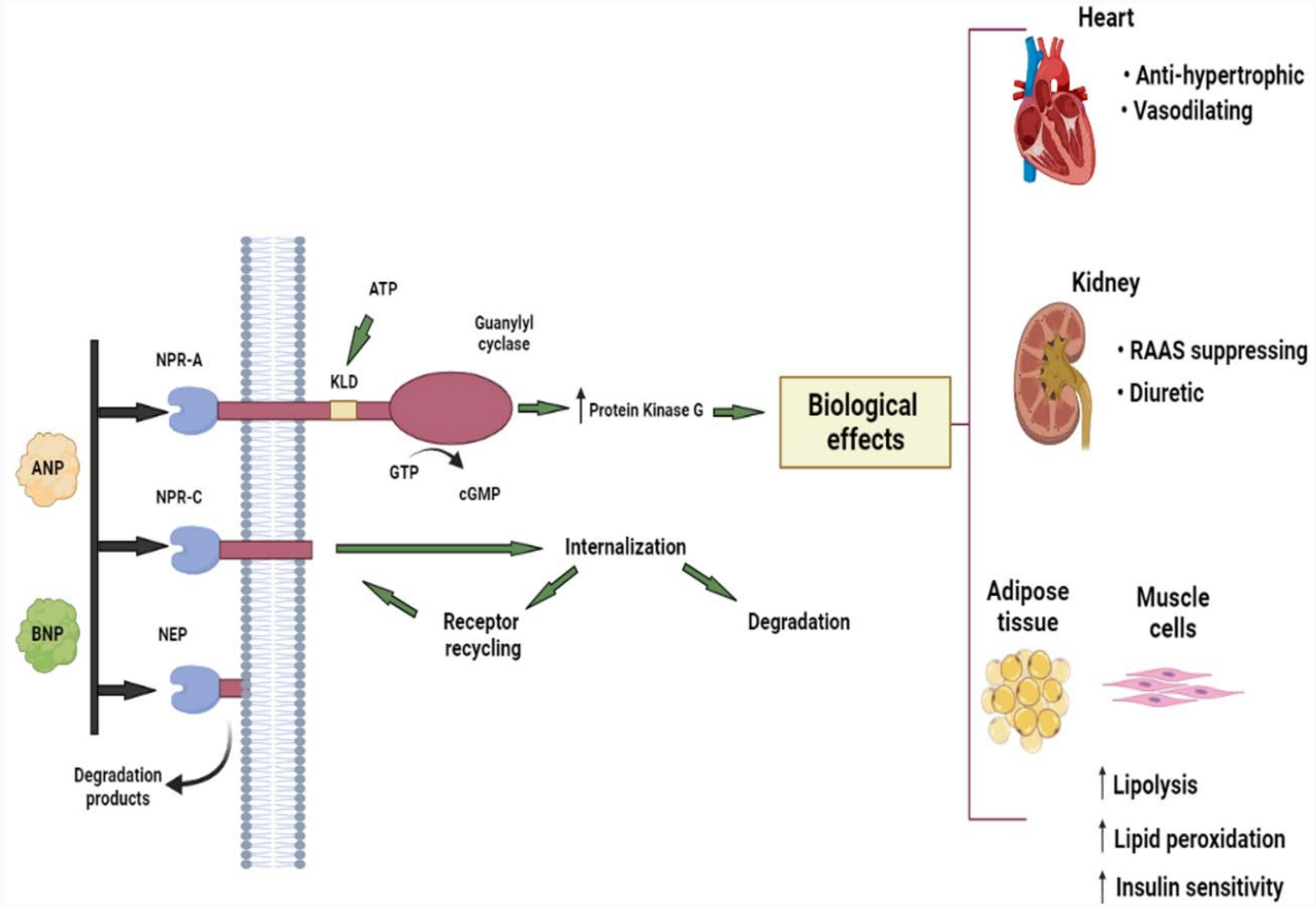

Figure 2: The ANP and BNP binds to the Natriuretic Peptide Receptor A (NPR-A) and stimulates the receptor's intrinsic guanylyl cyclase activity in an ATP-dependent manner. The biologic effects of cyclic Guanosine Monophosphate (cGMP) are mediated by cGMP-dependent protein kinase G or one or more Phosphodiesterase's (PDEs), or by direct action on effectors such as amiloride-sensitive sodium channels in the kidney. The receptor's Kinase-Like Domain (KLD) is required for ATP dependence. The Natriuretic Peptide Receptor C (NPR-C) binds to atrial natriuretic peptide, which is then internalised and degraded. It's possible that the C receptor has its own signalling functions. Finally, extracellular Neutral Endopeptidases (NEPs) in the kidney and vasculature may degrade atrial natriuretic peptide.

adjusting for age, left ventricular ejection fraction, and other factors, increasing plasma levels of MR-proANP independently predicted poor survival [23].

Mechanism of Action of ANP and BNP Peptides

Plasma membrane surface receptor are affected by natriuretic peptides which are present on the target cells. The Natriuretic Peptide Receptor (NPR)- A binds to ANP the most, with lower affinities for BNP and CNP. The NPR-A gene has the highest expression in the cardiovascular, circulatory, kidneys, suprarenal glands, and lungs, whereas the NPR-B gene has the highest expression in the brain [24]. The guanylate cyclase-associated receptors family includes the transmembrane proteins NPR-A and NPR-B. After the receptor binds to the ligand, guanosine triphosphate is changed into cyclic guanosine monophosphate, which starts the signal cascade in the cell that causes natriuretic peptides to have physiological effects [25]. Because its specifically involved in blood circulation to remove the natriuretic peptides (Transformation and degradation of the ligand-NPR-C complex occur), NPR-C is known as the elimination receptor. The kidneys and blood vessels also have neutral endopeptidase which can also remove natriuretic peptides [26] (Figure 2). The intrinsic guanylyl cyclase activity of the receptor is stimulated by the ANP, which binds to the NPR-A in an ATP-dependent manner. Cyclic Guanosine Monophosphate (cGMP) affects effectors directly, such as amiloride-sensitive sodium channels in the kidney, or indirectly through cGMP-dependent protein kinase G, one or more Phosphodiesterase's (PDEs), or both. The receptor's Kinase-Like Domain (KLD) is required for ATP dependence. ANP also removed from the circulation after binding to the NPR-C. Finally, extracellular neutral endopeptidases can remove ANP [24].

Prognostic and Diagnostic Mr-proANP and NT-proBNP Biomarker in HF

HF patients often have nonspecific signs and symptoms, making it difficult to distinguish between HF and other illnesses. Because of the variety of symptoms, definitive diagnosis and treatment are delayed [24]. The gold standard biomarkers in HF are natriuretic peptides (ANP and BNP). Increased ventricular production of ANP and BNP occurs as a result of the cardiac hypertrophy that occurs with myocardial failure. These peptides have been proven to be excellent diagnostic markers as well as useful parameters for figuring out how severe the disease can be [27]. BNP and its precursor N-terminal proBNP are the frequently analyzed natriuretic peptides used in the diagnosis of HF (NT-proBNP). ANP is currently regarded as inferior to BNP, owing to the fact that its assessment is thought to be less

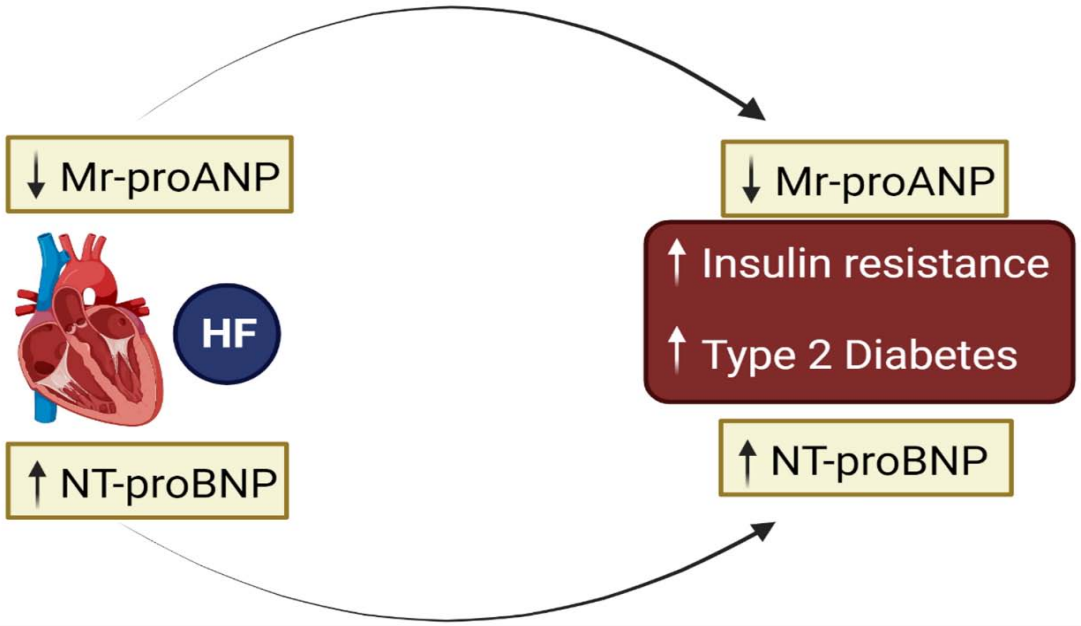

Figure 3: The level of MR-proANP and NT-proBNP linking the HF risk with type 2 diabetes patients. The level of Mr-proANP and NT-proBNP can be used as biomarker for detecting the earlier risk of HF in T2D patients.

repeatable [16,28]. In HF, ANP production increases in consequence to increased atrioventricular stretch, but because its half-life is only 2min to 5 min, it can be challenging to accurately measure circulating ANP concentrations [29]. ProANP, the 126-amino-acid prohormone of ANP, has a longer half-life that facilitates serum measurement.

Mr-proANP Biomarker in HF Patient with Diabetes

Now a days T2DM is considered as one of the most common metabolic diseases in the world. The function of natriuretic peptides in diabetes is unknown, despite the fact that they are involved in a number of metabolic and cardiovascular processes [30]. Previous evidence suggests that having a low ANP level raises the risk of T2DM and insulin resistance (Figure 3). It was also suggested that serum natriuretic peptide levels may be linked to the risk of developing diabetes. To determine the role of ANP in the emergence of diabetes, extended study is required [31]. HF significantly worsens the prognosis in patients with T2DM. MR-proANP is a useful biomarker for diagnosing HF in T2DM outpatients. Not much information is known about the diagnostic value of MR-proANP in the T2DM, even though the increase B-type natriuretic peptides was observed in the HF patients with preserved Ejection Fraction (HFpEF) [32]. However, HFpEF is challenging to diagnose, necessitating more study into HFpEF in T2D patients. Patients reporting dyspnea, which was uncommon among outpatients with T2DM, are diagnosed with HF using MRproANP, which also adds independent information and rules out HFrEF [33]. It shows that MR-proANP levels are strongly linked to occurrence of CVD in T2DM patients, and the MR-proANP with increased level and HFpEF patients are more susceptible to CVD condition compared to the patients who have suppressed level of Mr-proANP or patients with no history of HF [32].

NT-proBNP Biomarker in HF Patient with Diabetes

In both diabetic and nondiabetic subjects, NT-proBNP is well known prognostic and diagnostic HF biomarker [34]. The fraction of active BNP is low when the NT-proBNP levels are upregulated in the HF patients. The cardiac process of proBNP to BNP leads to the increase in circulating level in NT-proBNP in HF condition. Previous study reported that NT-proBNP was secreted more in HF patients and the diabetes was the commonly associated complication with higher release of NT-proBNP [35] (Figure 3). Earlier studies found that BNP and NT-proBNP are found to be in normal level in 30% of HF patients with preserved ejection fraction, while NT-proBNP are not always used as a reliable biomarker for HF diagnosis. This condition is similar in diabetic condition with the risk of CVD death or HF hospitalization since the HFPEF prevalence are very high in T2D compared to HF with reduced ejection fraction [36,37]. In addition to HF, NT-proBNP can provide quantitative information about the state of cardiovascular health across the entire CVD spectrum, and there is growing interest in their potential role as predictors and biomarkers of diabetes complications and mortality [5]. A clinical study of 315 T2D patients found that patients with albuminuria had higher NT-proBNP levels. Patients with albuminuria had higher NT-proBNP levels in a prospective study of 315 T2D patients. Furthermore, NT-proBNP was a best biomarker for predicting the CVD caused mortality comparable to that of microalbuminuria.

NT-proBNP was a strong predictor of all-cause and cardiovascular mortality, with a predictive value for all-cause mortality comparable to that of microalbuminuria [38]. Compare to the well-established cardiac biomarkers the NT-proANP predicts the accurate CVD events in T2D patients and similar to cholesterol or C-reactive protein, NT-proANP provide better prognostic information [39].

Future Perspective and Limitation

Our understanding of the roles of Mr-proANP and NT-proBNP in diabetes has greatly improved over the last decade, but many questions remain unanswered. More research is needed, in particular, to clarify the mechanisms of the natriuretic between diabetes and the heart. More reliable and specific assays for measuring both BNP and

NT-proBNP are required. Although the poor specificity of current assays does not impair BNP and NT-clinical proBNP's value as a predictor and biomarker of CVD, it severely limits our ability to understand underlying pathophysiological mechanisms and envision novel therapeutic strategies. In patients with acute chest pain, MR-proANP is a good predictor of future cardiovascular events. They have a higher predictive value than established biomarkers (BNP). Further research into the potential benefits of using such predictors in risk stratification and triaging of patients with chest pain is needed [40]. In an outpatient population with a high risk of HF, both plasma concentrations of NT-proBNP and MR-proANP added diagnostic information to patient-reported symptoms of HF, but NT-proBNP to a greater extent. The two natriuretic peptides had similar diagnostic performance for all types of HF and asymptomatic left ventricular systolic dysfunction, and they were linked to the same clinical and echocardiographic variables, with the exception of LVEF, which was linked to only NT-proBNP [41].

Conclusion

In patients with diabetic condition, heart failure and related sudden cardiac death are the leading causes of death. For T2D disorder patients, early diagnosis and accurate prognosis of HF can aid in the treatment process. In this process, Mr-proANP and NT-proBNP biomarkers CAN play an important role. Because these Mr-proANP and NT-proBNP biomarkers can reflect a variety of disease pathophysiological processes, they can still be used to identify high-risk groups in various metabolic disorder. The use of Mr-proANP biomarker in HF with T2D patients has a lot of potential, but more large-scale multi-center studies are needed to confirm their role. Recent studies demonstrating a role for MR-proANP and NT-proBNP in metabolism and T2D onset have expanded the interest in natriuretic peptide research beyond CVD and raised the possibility that new intervention strategies targeting the Mr-proANP and NT-proBNP system may be effective in lowering not only blood pressure and sodium retention, but also HF risk in diabetes patients. Mr-proANP and NT-proBNP used as a tool for early diagnosis, risk assessment, and guided intervention in CVD holds great promise for improving diabetes care.

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