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Brief Report

A Brief Report on Utility of N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) in Screening Patients at Risk of Atrial Fibrillation and Stroke

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N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a prohormone that is produced and released by the heart (ventricles) in response to alteration in pressure/strain/volume.[1-3] It is used as a biomarker of cardiac function and is involved in the regulation of fluid and electrolyte balance.[1-3] When the heart is under stress or is experiencing decreased blood flow, the ventricular myocardium releases the precursor molecule proBNP, which is then cleaved (by a membrane-bound enzyme called corin) into B-type natriuretic peptide (BNP) and NT-proBNP in equimolar amounts.[4,5] BNP is secreted into the blood and promotes vasodilation and diuresis, while NT-proBNP serves as a stable marker of cardiac function and is involved in the regulation of fluid and electrolyte balance.[6,7] NT-proBNP synthesized in the cardiac ventricles as a prepropeptide (134 amino acids) undergoes several post-translational modifications, including signal peptide cleavage, propeptide cleavage, and glycosylation, before being released as the mature 76-amino acid NT-proBNP molecule.[4,5] NT-proBNP is secreted into the bloodstream and is cleared primarily by the kidneys. NT-proBNP levels are influenced by a variety of factors, including age, sex, kidney function, and cardiac disease.[8,9] Elevated levels of NT-proBNP are associated with an increased risk of cardiovascular events, such as heart failure, atrial fibrillation and stroke, and can be used as a diagnostic tool to identify individuals at risk of these conditions.[6,10-12] The concentration NT-proBNP can be measured in serum/plasma samples. The assays for NT-proBNP measurement typically use immunoassay techniques, such as Enzyme-Linked Immunosorbent Assay (ELISA) or Chemiluminescence Immunoassay (CLIA), which rely on the binding of specific antibodies to the NT-proBNP molecule. These assays are highly sensitive and specific, with low limits of detection and high precision, making them valuable tools for the diagnosis and management of cardiovascular disease.[11,12]

Atrial Fibrillation (AF) is a common and growing health concern affecting millions of people worldwide. AF is the most common sustained cardiac arrhythmia in clinical practice, affecting millions of people worldwide.[13-15] The incidence of AF has been increasing in recent years due to aging populations, increased prevalence of cardiovascular risk factors, and paraphs consequence to improved detection methods.[14,16] The incidence of AF varies according to age, gender, and underlying medical conditions. In general, the incidence of AF increases with age, with a sharp rise in incidence after the age of 60. AF is more common in men than in women, but the gender gap narrows with increasing age.[13-16] The incidence of AF is strongly influenced by underlying medical conditions, such as hypertension, heart failure, coronary artery disease, valvular heart disease, and obesity. Individuals with these conditions are at higher risk of developing AF, and the incidence of AF is further increased in those with multiple risk factors.[13,16] Studies have reported varying incidence rates of AF, depending on the population studied, the diagnostic methods used, and the duration of follow-up. In the general population, the incidence of AF is estimated to be around 1-2% per year, with a lifetime risk of approximately 25%. The incidence of AF is higher in individuals with underlying medical conditions, such as heart failure or hypertension (10-15% per year).[16,17] The incidence of AF is also influenced by ethnicity, with some studies reporting higher incidence rates in white populations compared to other ethnic groups. However, the reasons for these differences are not fully understood and require further investigation. Early detection and effective management of AF are essential for reducing the burden of this condition on individuals and healthcare systems.

Stroke is a one of the leading causes of morbidity and mortality worldwide and represents a significant public health concern. The incidence of stroke varies according to age, gender, and geographical region.[18,19] In general, the incidence of stroke increases with age, with the highest incidence rates observed in individuals over 65 years of age. Similar to AF, the incidence of stroke is also higher in men than in women, and this gender gap narrows with increasing age. The incidence of stroke varies across different geographical regions, with higher rates reported in low- and middle-income countries compared to high-income countries.[20,21] This may be due to differences in risk factors, access to healthcare, and other socioeconomic factors. Several modifiable risk factors are known to increase the incidence of stroke, including hypertension, diabetes, smoking, hyperlipidemia, obesity, physical inactivity, and excessive

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alcohol consumption.[20-22] Effective management of these risk factors can significantly reduce the incidence of stroke. The incidence of stroke has been declining in recent years, likely due to improved management of risk factors and better access to healthcare. However, stroke remains a significant cause of morbidity and mortality worldwide, with significant implications for individuals, families, and healthcare systems. Early detection and effective management of risk factors are essential for reducing the incidence of stroke and improving health outcomes together with targeted research to better understand the factors contributing to the incidence of stroke and developing effective innovative strategies for prevention and management of stroke.

A recent report analysing the LOOP study[23,24] has shed light on the potential utility continuous implanted recording device based on NT-proBNP levels for identifying individuals at higher risk of developing AF and associated clinical events such as stroke. This study highlights that NT-proBNP levels above the median are associated with an increased risk of AF diagnosis and subsequent clinical events, including stroke, systemic embolism, cardiovascular death, and all-cause death. Of particular interest is the finding that implantable loop recorder (ILR, a form of cardiac monitor) screening,[23,24] compared to usual care, was associated with significant reductions in Stroke/Systemic Embolism (SE) and stroke/SE/cardiovascular death among participants with NT-proBNP levels above the median threshold (>15 pmol/L). However, no risk reduction in all-cause death was observed in either NT-proBNP subgroup for ILR versus control group. This suggests that targeted ILR screening may be a useful tool for preventing and reducing the incidence of specific clinical events in individuals with higher NT-proBNP levels. The results of this study have important clinical implications. Given the association between NT-proBNP levels and the risk of AF diagnosis and subsequent clinical events, it may be worthwhile to consider including NT-proBNP measurements as part of routine screening for AF in older adults. Additionally, these findings support the use of targeted ILR screening in individuals with higher NT-proBNP levels to prevent and reduce the incidence of specific clinical events. It is worth noting that this study has some limitations. For instance, the participants in this study were older adults, and the findings may not be generalizable to younger populations. Additionally, the study did not examine the potential mechanisms underlying the relationship between NT-proBNP levels and clinical events. Also, the potential risk to the patients from the ILR is unclear on a long-term use and paraphs a non-invasive approach would be preferable and clinically compatible here.

While NT-proBNP is a widely used biomarker for assessing heart failure, AF and other cardiovascular conditions, it is not without its limitations.[12,25] Some of the limitations of using NT-proBNP as a biomarker are: 1) Lack of specificity: Elevated levels of NT-proBNP can be seen in conditions other than heart failure, such as pulmonary hypertension, renal failure, and sepsis, which can lead to false positives and misdiagnosis. 2) Variability in results: NT-proBNP levels can be affected by several factors, including age, gender, body mass index, renal function, and medications, which can result in variations in results and limit its usefulness as a consistent biomarker. 3) Cost: The cost of NT-proBNP testing can be a limitation, particularly in resource-limited settings where access to expensive diagnostic tests is limited. 4) Lack of standardized reference ranges: There is a lack of consensus on the optimal reference range for NT-proBNP, which can lead to differences in interpretation and limit its clinical usefulness. This can also lead to differences in results and interpretation, making it difficult to compare data across studies and institutions. 5) Limited utility in certain populations: NT-proBNP may not be as useful in certain populations, such as patients with obesity or chronic kidney disease, where levels may be artificially elevated or masked, respectively. 6) Preanalytical factors: The measurement of NT-proBNP can be affected by preanalytical factors such as sample handling and processing, storage conditions, and hemolysis, which can lead to inaccurate results. 7) Interference from other substances: Certain substances, such as heterophilic antibodies, can interfere with the measurement of NT-proBNP and result in false positives or negatives. 8) Analytical factors: The analytical method used to measure NT-proBNP can affect the accuracy and precision of the results. Different assays may have different sensitivities and specificities, leading to variations in results and affecting the clinical interpretation of the biomarker. Hence it is essential to consider these limitations and use NT-proBNP only in conjunction with other clinical and diagnostic tools to arrive at a definitive diagnosis.

The measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a biomarker for heart failure and other cardiovascular conditions requires the use of laboratory techniques such as immunoassays.[12,25,26] However, these techniques also have some limitations, including: 1) Variability in assay performance: Different immunoassays can have variable performance characteristics, such as sensitivity, specificity, and precision, which can affect the accuracy and reliability of the results. This can be compounded by the lack of standardization in the measurement of NT-proBNP. 2) Interference from other substances: As with any immunoassay, there is a risk of interference from substances that may cross-react with the antibodies used in the assay, leading to false positive or negative results. 3) Influence of preanalytical factors: The accuracy and reliability of NT-proBNP measurement can be influenced by preanalytical factors such as sample handling, storage, and processing. For example, hemolysis, lipemia, and other factors can interfere with the measurement and lead to inaccurate results. 4) Influence of biological factors: NT-proBNP levels can be influenced by biological factors such as age, sex, renal function, and comorbidities. These factors can affect the interpretation of NT-proBNP results and limit its diagnostic

utility. The sensitivity of kits used to measure N-terminal pro-B-type natriuretic peptide (NT-proBNP) can vary depending on the manufacturer and the type of assay used. Sensitivity refers to the lowest concentration of NT-proBNP that can be reliably detected by the assay. For example, the sensitivity of the Roche Elecsys NT-proBNP assay is reported to be 5 pg/mL, while the sensitivity of the Beckman Coulter Access NT-proBNP assay is reported to be 20 pg/mL. Other assays may have different sensitivities. It is important to note that sensitivity alone does not determine the accuracy or reliability of an assay. Other factors such as specificity, precision, and interference from other substances can also affect the performance of the assay. In addition, the clinical utility of NT-proBNP as a biomarker depends not only on the sensitivity of the assay but also on its ability to differentiate between different clinical conditions and its correlation with disease severity and prognosis. Therefore, it is important to interpret the results in the context of the patient's clinical history and other diagnostic tests.

Several clinical conditions can influence the circulatory level of NT-proBNP.[27,28] Clinical conditions which can elevate NT-proBNP include: 1) Heart failure: The most common cause of elevated NT-proBNP levels is heart failure. As the heart struggles to pump blood effectively, the levels of NT-proBNP increase in response to the increased pressure and volume overload. 2) Acute coronary syndrome: NT-proBNP levels can also be elevated in patients with Acute Coronary Syndrome (ACS), which includes unstable angina and myocardial infarction (heart attack). 3) Pulmonary hypertension: NT-proBNP levels can be elevated in patients with pulmonary hypertension, a condition in which the blood pressure in the arteries that supply the lungs is abnormally high. 4) Atrial fibrillation: NT-proBNP levels can be elevated in patients with atrial fibrillation, a type of irregular heartbeat. 5) Renal failure: NT-proBNP levels can be elevated in patients with renal failure, as the kidneys play a role in removing the peptide from the bloodstream. 6) Sepsis: NT-proBNP levels can also be elevated in patients with sepsis, a life-threatening condition that occurs when the body's response to an infection causes organ dysfunction. 7) NT-proBNP levels can also be elevated in patients with other conditions such as valvular heart disease, cardiomyopathy, and myocarditis. Hence it is important to note that the clinical context and other diagnostic tests are necessary to interpret NT-proBNP levels and to differentiate between different clinical conditions.

In contrast some clinical condition can lead to decrease in NT-proBNP levels[29,30] and these include: 1) Obesity: Studies have shown that obese individuals may have lower NT-proBNP levels compared to non-obese individuals. This may be due to factors such as increased adipose tissue mass, insulin resistance, and inflammation. 2) Hypothyroidism: NT-proBNP levels may be decreased in patients with hypothyroidism, a condition in which the thyroid gland does not produce enough thyroid hormone. This may be due to alterations in cardiac function and metabolism. 3) Use of certain medications: Some medications, such as Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs), have been reported to decrease NT-proBNP levels in patients with heart failure. This may be due to their effects on the renin-angiotensin-aldosterone system, which plays a role in regulating NT-proBNP production.

In summary, the interpretation of NT-proBNP levels should always be done in conjunction with other clinical information and not in isolation. Further the potential utility of the continuous monitoring medical devices together with biochemical markers in patient care is promising and efforts to develop non-invasive approaches should be considered, which in my option offers greater dexterity in delivering clinical care.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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