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Heart failure biomarkers in hemodialysis patients

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ABSTRACT

The *diagnosis of end-stage renal disease (ESRD) is made when the estimated glomerular filtration rate is less than 15 mL/min/1.73 m^2. Most patients with that stage of chronic kidney disease (CKD) are eligible for renal replacement treatment, which includes kidney transplantation, hemodialysis and peritoneal dialysis. It is well recognized that CKD raises the risk of cardiovascular disease and is linked to a higher cardiovascular death rate in this population. Additionally, the largest risk of cardiovascular events is seen in ESRD patients. Heart failure (HF) and dangerous arrhythmias, which are more common in the advanced stages of CKD, are two additional causes of cardiovascular death in addition to atherosclerosis-related complications such as myocardial infarction and stroke. In this review the significance of natriuretic peptides and other HF biomarkers in hemodialysis patients, as tools for cardiovascular risk assessment will be discussed.*

Keywords: heart failure, hemodialysis, biomarker, chronic kidney disease, natriuretic peptides

Introduction

According to the latest classification, edited by the Kidney Disease: Improving Global Outcomes Work Group (KDIGO) in 2012, chronic kidney disease (CKD) is defined as the presence of a reduced kidney function (i.e., an estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) and/or albuminuria, a strong marker of kidney damage [1]. Based on this classification the end-stage renal disease (ESRD) is diagnosed when eGFR value is < 15 mL/min/1.73 m^2. Moreover, in this stage of CKD, patients are qualified for renal replacement therapy (RRT) including dialysis (hemodialysis, peritoneal dialysis) and pre-emptive renal transplantation. The number of patients receiving RRT exceeds 2.5 million and is expected to double to 5.4 million by 2030 [2]. Reasons for the increasing incidence and prevalence of advanced CKD, among others, include aging populations, the increasing prevalence of type 2 diabetes and hypertension, and low detection rate and therapeutic inertia in the early stages of CKD [3, 4]. CKD has also been recognized as a risk factor for cardiovascular disease (CVD) independent of other conventional risk factors [5]. CKD is associated with an increased risk for CVD mortality and the risk is the highest in dialysis patients [6]. Heart failure (HF) and dangerous arrhythmias, in the advanced stages of CKD, are major causes of cardiovascular death in addition to an increased risk of atherosclerosis-related complications such as myocardial infarction and stroke. If registry studies are excluded, the meta-analysis indicates that around half (49%) of individuals with HF have CKD [7]. In a sizable population-based research study conducted in the United States, the incidence of HF in patients with CKD was 18/1000 person-years [8]. HF is more common in individuals with declining renal function; 44% of dialysis patients have HF, and half of them have a lower left ventricular ejection fraction (LVEF) [9]. Patients with CKD with HF

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have a poor prognosis that gets worse as renal function declines [10]. HF is a clinical syndrome rather than a single medical entity. It is characterized by cardinal symptoms, such as fatigue, ankle swelling, and dyspnea, which may be accompanied by indicators, such as peripheral edema, pulmonary crackles, and high jugular vein pressure. It is caused by an anomaly in the structure or function of the heart that leads to high intracardiac pressures and/or insufficient cardiac output while the body is at rest or exercising. The existence of HF symptoms and/or indications along with objective proof of heart dysfunction serve as the basis for the diagnosis of HF. In certain instances, natriuretic peptides (NPs) must be determined to diagnose a patient; nevertheless, the test's effectiveness is independent of their availability. A diagnosis of HF is improbable if the plasma concentration of B-type natriuretic peptide (BNP) is less than 35 pg/mL, N-terminal pro-B-type natriuretic peptide (NT-proBNP) is less than 125 pg/mL, or mid-regional pro-atrial natriuretic peptide (MR-proANP) is less than 40 pmol/L [11, 12]. Furthermore, it is advised that echocardiography ought to be utilized as the primary study method to evaluate heart function. Echocardiography not only measures the LVEF but also determines chamber size, eccentric or concentric left ventricular hypertrophy (LVH), abnormalities in regional wall motion that may indicate the presence of coronary artery disease, Takotsubo syndrome, or myocarditis, right ventricle function, pulmonary hypertension, valvular function, and diastolic function markers [13]. However, it is advised to get a chest X-ray to rule out other possible reasons for dyspnea, such as pulmonary illness. Additionally, it might offer HF-supporting data (such as cardiomegaly or pulmonary congestion) [14]. The relevance of NPs, with a focus on B-type (or brain-type) NPs (BNP) and other HF biomarkers, in patients with ESRD will be outlined in this study along with their possible use as risk stratification biomarkers in therapeutic therapy. The sources of HF biomarkers and the influence of hemodialysis on their levels are shown in the Central illustration.

Natriuretic peptides

While an elevated serum concentration of NPs calls for additional diagnostic testing to establish HF, a normal level of NPs helps rule out HF [15]. It has been discovered that the kidneys play a role in the excretion of NPs. It is debatable whether NPs should be assessed in this population because a high concentration of NPs can be seen in a significant number of individuals with kidney failure [16]. A-type (ANP), B-type (BNP), C-type (CNP), D-type (DNP), V-type (VNP), and urodilatin are the six human cardiovascular NPs that are now recognized [17–20]. It has been discovered that NPs establish an intramolecular disulfide link and retain their intact ring shape, which includes 17 amino acid (aa) residues and is likely crucial for receptor binding [18, 19]. At least three different kinds of NP clearance receptors (NPRs) have been found, according to the literature. NPR-A and NPR-B are membrane-bound guanylyl cyclase-coupled receptors that are involved in CNP clearance and preferentially bind to both ANP and BNP [19]. The synthesis of 3',5'-cyclic guanosine monophosphate (cGMP) is linked to the biological action [18, 21]. On the other hand, NPR-C has been discovered to lack a guanylyl cyclase domain. This kind of receptor suppresses membrane adenylyl cyclase activity, which is crucial for controlling cell division. Additionally, NPR-C exhibits affinity for different NPs in the following order: ANP > CNP > BNP, and it is engaged in other processes such the clearance of NPs [21]. It is important to emphasize that the effects of renin–angiotensin–aldosterone system activation are counteracted by both BNP and ANP. NPs have a hypotensive impact because they cause vasorelaxation, enhance natriuresis and diuresis, and so on [18, 19, 22]. Compared to ANP, BNP exhibits slower action and greater stability in vitro. Guidelines on heart failure from the European Society of Cardiology in 2021 [15] BNP is crucial for laboratory evaluation, risk assessment, and follow-up in HF patients [17, 18]. In response to ischemia, an inflammatory process, increased wall stretch, and sympathetic system hyperreactivity, cardiomyocytes excrete NT-proBNP, an inactive peptide that serves as a marker of pathologically elevated cardiac filling pressures linked to myocardial stress [19, 24]. BNP and NT-proBNP have half-lives of roughly 20 minutes and one to two hours, respectively [17, 19]. There is no proof that ESRD patients experience this period longer than the general population [25]. Conversely, longer "effective" or "functional" half-lives have been noted for them [26]. The kidneys eliminate both NPs either as metabolites or in their active state [19]. While they do not affect the clearance of NT-proBNP, NPR-C and neutral endopeptidase are engaged in the clearance of BNP [27]. Consequently, it appears that NT-proBNP clearance may be more affected by significantly reduced renal function than by BNP [19]. Finally, it must be noted that the target NP

and other metabolites, as well as its precursor, are measured by the current NPs assays. For example, BNP assays can identify proBNP in addition to BNP1-32 and other metabolites such BNP3-32, BNP4-32, and BNP5-32 [23, 28]. Analyzing both NT-proBNP and proBNP is also possible using NT-proBNP assays. Furthermore, NPs levels may be miscalculated if they are glycosylated, as this can influence the antibody binding process [23, 28]. The endogenous amount of glycosylated NT-proBNP was shown to be increased in hemodialysis patients, and existing techniques were unable to detect it [29]. Furthermore, it has been noted that in patients under dialysis, NT-proBNP levels were significantly higher (pre-dialysis 4079 pg/mL, post-dialysis 2759 pg/mL, $p < 0.001$) [30]. It was shown in another study that hemodialysis patients with established CVD or diabetes mellitus had BNP levels that were considerably greater than those of people without these diseases [31]. Furthermore, the scientists demonstrated that while BNP levels in hemodialysis patients without a history of CVD declined during dialysis, they remained higher than in healthy individuals. However, in patients with stage 4 and 5 CKD, both BNP and NT-proBNP were helpful in predicting the time to the onset of RRT, according to some investigators [32]. It is important to emphasize that the concentrations of NT-proBNP before and after dialysis, respectively, were linked with the extracellular/total body water ratio (ECV/TBW) and relative overhydration (ROH) [33, 34]. To determine whether there is a relationship between volume status and changes in NPs levels in ESRD patients, more research is required. The available information regarding the usefulness of NPs cut-off values for forecasting major adverse events is debatable because the majority of trials were underpowered, single-center, and had insufficient follow-up to yield insightful outcome data. Furthermore, it has been discovered that individuals receiving recurrent hemodialysis may have different levels of NPs depending on the type of membrane utilized in the dialyzer. Low-flux membranes had the opposite effect on the concentration of NT-proBNP as they were linked to lower levels of BNP. On the other hand, BNP concentration in patients was decreased by high-flux membranes, although NT-proBNP was unaffected (Table 1) [35, 36].

The findings of longitudinal studies that use a small number of repeat NPs measurements to examine the correlation between changes in peptide concentration and changes in the risk of fatal events provide the strongest evidence for the potential role of BNP as biomarkers of cardiac risk in the population receiving renal dialysis. In both incidents and prevalent hemodialysis patients, these investigations showed a direct correlation between changes in BNP concentration and changes in the risk of cardiovascular and all-cause mortality [37]. Although these studies represent a significant first step toward defining the biomarker's clinical application in dialysis, they are constrained by the absence of repeatable measures, the short time to event, and the accuracy measures (specificity and sensitivity), all of which are necessary to move this promising marker closer to the clinical application [38].

BNP and NT-proBNP are useful in predicting HF and a worse prognosis in ESRD [39]. Nevertheless, different results have been reported in multiple trials, therefore there is no agreement on the cut-off value for NPs concentration to indicate worse outcomes [40, 41]. Lastly, depending on the concentration of NPs in ESRD, there is currently no evidence to recommend any particular treatment. There is no agreement on the best time when the assessment of NPs in dialysis patients should be performed in everyday clinical practice. It was found that NT-proBNP levels evaluated 30 minutes after dialysis had a greater value in predicting left ventricle dysfunction than NT-proBNP levels tested before dialysis in one study involving children receiving hemodialysis [42]. On the other hand, the results of the other trial showed no discernible variation in mortality estimates between the pre- and post-dialysis assessments [30]. Moreover, dialysis may also have an impact on the cut-off thresholds. Arteriovenous fistulas can also have cardiotoxic consequences in hemodialysis patients, which could have an impact on how BNP quantities are interpreted. Because it is currently challenging to suggest therapeutic solutions based on high NPs levels in patients with severe CKD, further evidence is therefore required. The most common clinical conditions affecting NPs concentration are presented in Table 2.

Troponin

Particularly when applied within the diagnostic threshold of the 99th percentile of healthy controls, cardiac troponin T (cTnT) and I (cTnI) are sensitive indicators of cardiac damage [43]. It is still debatable how cardiac troponins should be interpreted in CKD patients receiving hemodialysis. It has been suggested in the literature that in CKD patients with non-acute coronary syndrome, decreased urine clearance is unlikely to be the main cause of

an increase in cTnT or cTnI [44]. It is important to emphasize that cTn is indicative of LVH, clinically silent ischemia, or myocyte destruction [45]. However, in the ESRD population, increased cardiac troponins are potent predictive indicators. After 1, 2, and 3 years of follow-up in the dialysis group, Apple et al. [46] demonstrated that an elevated cTnT above the 99th percentile was predictive of an increased risk of death. Furthermore, compared to those with undetectable cTnT levels, the all-cause mortality was at least 2.5–5 times greater in those with cTnT > 99th percentile. An increased cTnT > 0.1 lg/l can identify a subgroup of asymptomatic ESRD patients with poor survival and a higher risk of cardiac death, according to a meta-analysis by Khan et al. [47]. Additionally, in asymptomatic hemodialysis patients, serially increasing cTnT ≥ 0.4 ng/mL over 12 months is similarly indicative of an increased risk of cardiovascular events and mortality [48].

The use of cTnT as a biomarker for mortality risk classification in patients with ESRD has been approved by the Food and Drug Administration. Comparably, the clinical application of cTnT for mortality and cardiovascular risk stratification has also been advised by the Kidney Disease Outcomes Quality Initiative (KDOQI) [49]. Studies that looked at how the dialysis process affected cTn levels, however, showed different data; some reported an increase in cTnT post-dialysis, while others showed a decrease in cTnI levels [50]. It seems to be reasonable to assess cardiac troponins on predialysis samples because high-flux dialysis membranes seem to remove both troponins [51]. The National Academy of Clinical Biochemistry's clinical practice guideline states that in the population of people with renal failure who exhibit symptoms, electrocardiographic findings, or other clinical evidence suggestive of myocardial ischemia (Level of evidence grade A), measurement of cardiac troponins is warranted to evaluate acute myocardial infarction [52]. Monitoring cardiac troponins at regular intervals may potentially be beneficial for dialysis patients. This makes it possible to distinguish between acute and chronic elevation in addition to monitoring changes over time. Longitudinal cohort studies are required to move troponin testing in clinical dialysis practice. These studies will clarify the optimal interpretation of the test, including whether to use an absolute cut-off or relative change between serial measurements, the frequency of measurements, the time between an abnormal test and an unfavorable outcome, and the therapeutic targets.

The soluble suppression of tumorigenicity 2 protein

A member of the interleukin 1 receptor family, suppression of tumorigenicity 2 protein (ST2) is expressed in a variety of cells under various circumstances, including stress and inflammation. It occurs in transmembrane (ST2L) and soluble (sST2) isoforms. Interleukin 33 (IL-33) functions as an ST2 ligand and binds to ST2L to cause nuclear signaling and immunomodulatory effects in a variety of cells, including immune, tumor, and cardiac cells. When sST2 is delivered into the bloodstream, it acts as an IL-33 "decoy" receptor, blocking both positive effects and IL-33/ST2L signaling [53]. It can be thought of as an indicator of inflammation, remodeling, and fibrosis. As a novel biomarker for cardiovascular events in individuals with HF, ST2 is widely recognized [54]. Additionally, ST2 shows increasing promise for monitoring and optimizing HF patient care [55]. In the ESRD population, the biomarker's function was validated. In addition to adding predictive value to previously identified prognostic indicators, its pathophysiological features and independence of renal function enable more accurate identification of patients at high risk for hospitalization, cardiovascular and all-cause mortality [56]. In chronic hemodialysis patients, ST2 was found by Obokata et al. [56] to be an independent prognostic factor with a superior predictive ability than BNP. In dialysis patients, ST2 was found to be a predictor of both cardiovascular and all-cause mortality in another investigation. Furthermore, when combined with BNP, this molecule was linked to higher predictive power but had no greater predictive value than BNP [57]. However, regardless of whether a low-flux or high-flux dialyzer was utilized, the sST2 level variation was less than 5% before vs. after the dialysis session (Table 1) [58]. Consequently, sST2 requires further investigation and more frequent usage in clinical practice among hemodialysis patients due to its significant marker characteristics (low biological variability and independence of gender, age, renal function, and dialysis procedure).

Galectin-3

The expression of galectin-3 varies based on the type of tissue; nevertheless, stress or injury to the tissue might stimulate its expression. Overexpression and secretion of galectin-3 have been linked to several illnesses and have been thoroughly investigated concerning fibrosis and

Table 1. Potential utility of cardiac biomarkers in the hemodialysis population

Biomarker	Source	Diagnosis values	Prognostic value	Affected by hemodialysis
BNP and NT-proBNP	Ventricular cardiomyocyte	Yes [34]	Yes [34]	Yes/Slightly [35]
cTnT and cTnI	Cardiomyocyte	Yes [45]	Yes [45, 46]	Slightly [50]
sST2	Cardiomyocyte	Probable [55]	Yes [55, 57]	No [57]
	Endothelial cell			
	Fibroblast			
GDF15	Cardiomyocyte	Probable [67]	Yes [67, 69]	N/A
Galectin-3	Macrophages, neutophils, endothelial cells	No [61]	Yes [61, 62]	Yes [62]
H-FABP	Cardiomyocyte	Probable [72]	Yes [72]	Yes [72]

cTnT — cardiac troponin T; cTnI — cardiac troponin I; BNP — B-type natriuretic peptide; NT-proBNP — N-terminal pro B-type natriuretic peptide; ST2 — suppression of tumorigenicity 2; sST2 — soluble ST2; GDF15 — growth and differentiation factor 15; H-FABP — heart-type fatty acid binding protein; N/A — not available

inflammation, where it has been shown to play a key role in the pathophysiological pathways that contribute to the onset and progression of HF [59]. Furthermore, it has been shown that galectin-3 plays a role in the formation of fibrosis in the kidney and liver [60]. When combined, these findings imply that galectin-3 might play a role in the onset of HF. A galectin-3 blocker is hypothesized to delay the course of HF and potentially lower morbidity and death associated with the disease. Liu et al. [55] discovered that higher galectin-3 concentrations were linked to an increased risk of cardiovascular death rather than all-cause mortality in a prospective Chinese cohort of maintenance hemodialysis patients followed for up to 60 months. Higher serum levels of galectin-3 did not appear to be associated with a higher risk of cardiovascular death in hemodialysis patients, according to a recent meta-analysis and the findings of the AURORA trial (Table 1) [62, 63]. These findings imply that significantly elevated galectin-3 may represent activated fibrogenesis applicable to risk stratification in the dialysis population, hence suggesting the possibility that anti-fibrotic medication could be advantageous for preserving CVD in these individuals. However, following hemodialysis session, there is a direct decrease in this biomarker's level.

Growth differentiation factor 15

A protein named growth differentiation factor 15 (GDF15) was recognized as a potential biomarker of CVD and mortality in the general population [64]. Most tissues have a modest expression of GDF15 in physiologic conditions [65]. Many different tissues, such as activated macrophages, cardiomyocytes, and vascular smooth muscle cells, potently upregulate its synthesis after injury, ischemia, and other types of oxidative and/or metabolic stress [66]. GDF15 was linked to a greater frequency of HF and LVH in the general population [67]. Higher levels of GDF15 were linked to a higher mortality risk in the hemodialysis population, regardless of sociodemographic and comorbidities variables, according to the multicenter MADRAD trial [68]. Furthermore, Breit et al. [69] discovered that subclinical atherosclerosis and an increased risk of mortality were linked to gradually increasing GDF15 levels, or every 10 ng/mL rise. Conversely, Lee et al. [70] discovered a relationship between the two-year mortality rate in patients with ESRD and the GDF15/albumin ratio at the beginning of the first maintenance hemodialysis. Furthermore, this biomarker's predictive value is superior to GDF15 alone (Table 1). Thus, the recently developed biomarker GDF15/albumin might support medical professionals in anticipating early mortality and offer opportunities to look for modifiable factors to prevent early mortality in this population.

Heart-type fatty acid binding protein

Heart-type fatty acid binding protein (H--FABP), which is produced in cardiac cells, can detect extremely early cases of myocardial ischemia in humans [71]. Even in patients who tested negative for troponin, Niizeki et al. [72] demonstrated that greater H-FABP levels upon hospital admission were linked to a higher risk of mortality and non-fatal cardiac adverse events. This biomarker was significantly increased in patients with ischem-

ic and dilated cardiomyopathy. Moreover, the level of H-FABP correlated significantly with the LVEF and demonstrated a parallel increase according to the New York Heart Association stages I–IV [72]. In the hemodialysis population, H-FABP decreased after the procedure due to increased clearance related to the total blood processed and hemodialysis treatment time. On the other hand, the level of this biomarker increased with increasing ultrafiltration volume, presumably secondary to hemoconcentration. It is uncertain how the level of H-FABP influences short- and long-term hemodialysis patient prognosis (Table 1) [73].

Conclusions

The analysis of the biomarkers of HF offers great potential for more detailed and precise diagnostic and risk stratification in hemodialysis patients. It has been proved, that the glomerular filtration rate affects the NPs cut-off value. sST2 is superior in comparison to other HF biomarkers in establishing diagnosis and prognosis in patients with ESRD and HF but it is still too early to use its concentration to guide therapeutic strategies. For a proper evaluation of the further clinical benefits of novel cardiovascular biomarkers in the diagnosis and management of the hemodialysis population with HF, more prospective studies will be required.

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Table 2. Clinical conditions affecting B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide concentrations

Increased levels	Decreased levels
Heart and circulation	Flash pulmonary oedema
Acute or chronic heart failure	Constrictive pericarditis
Acute myocardial infarction	Obesity
Pulmonary embolism	
Myocarditis	
Atrial fibrillation	
Ventricular tachyarrhythmias	
Valvular heart disease	
Pulmonary hypertension	
Other	
Senility	
Stroke	
Septic shock	
Renal failure	
Hyperthyroidism	
Liver cirrhosis	
COPD	
Cushing's syndrome	
Subarachnoid hemorrhage	

COPD — chronic obstructive pulmonary disease

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