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White Paper

Residual Renal Function in Dialysis: Toward Understanding its Importance and Simplifying its Assessment – the Potential Role of Beta-trace Protein

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Answers for life.

Introduction

Reduced renal function is associated with an increased risk of all-cause and cardiovascular mortality and has a significant negative impact on a patient's quality of life in the advanced stages.[1–5] Alarmingly, the prevalence of end-stage renal disease (ESRD) has increased more than 10-fold in the last 30 years in the United States.[4] As a result, the use of renal replacement therapies, such as hemodialysis, peritoneal dialysis, and kidney transplants, has risen dramatically, with an estimated 1.9 million patients undergoing renal replacement therapy worldwide annually.[4]

The major goals of dialysis treatment are to remove excess fluid and reduce the level of uremic toxins. Despite advances in technology, dialysis can only achieve approximately 15% of native kidney urea clearance and even lower clearance for many other uremic toxins.[6,7] Native kidney function in dialysis patients, also known as residual renal function (RRF), can contribute significantly to removal of these toxins and help with maintaining fluid balance. As a result, presence of RRF is associated with improved outcomes, better quality of life, and a survival benefit in patients receiving peritoneal dialysis (for example, in the Canada and USA [CANUSA] study; Table 1).[8–13] The pivotal role of RRF in hemodialysis patients has been well documented in studies such as the Netherlands Cooperative Study of Dialysis (NECOSAD)[14,15] and the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) (Table 1).[1]

Changes in RRF significantly affect the health of the hemodialysis patient, as the kidneys contribute to a variety of physiological processes, including:[8–10]

- Solute clearance by filtration (e.g., urea and creatinine) and secretion (e.g., p-cresol sulfate and indoxyl sulfate)
- Maintenance of fluid balance (with particular relevance to blood pressure control and reduction in cardiovascular disease)
- Phosphorus control
- Removal of uremic toxins such as phosphate

Furthermore, hemodialysis patients with preserved RRF have higher levels of hemoglobin due to higher levels of endogenous erythropoietin. These patients have been found to experience an improved quality of life compared with patients who have lower levels of RRF.[18]

It is often thought that RRF declines rapidly in hemodialysis patients. However, data show that RRF may be present for longer than previously suspected, naturally declining over an extended period of time (Figure 1). A large proportion of hemodialysis patients have significant RRF even after 5 years on therapy.[14,19] Nevertheless, the natural, gradual decrease in RRF contributes significantly to anemia, inflammation, and malnutrition and is a strong predictor of mortality.[9,10] Indeed, it appears that the rate of decline in RRF may be a greater predictor of outcome than baseline RRF;[12] a recent study of patients undergoing peritoneal dialysis followed for 4 years found that those patients with the greatest rate of decline in RRF had the lowest survival rate.[12]

Table 1. Importance of RRF on outcomes in peritoneal dialysis and hemodialysis patients: data from the CANUSA, NECOSAD, and CHOICE studies.[1,9–17]

Peritoneal Dialysis	Hemodialysis
• The CANUSA study demonstrated that for every 0.5 mL/min/1.73 m^2 of additional glomerular filtration rate (GFR), there was a 9% decreased risk of death.[15]	• The NECOSAD study demonstrated that preventing or delaying the complete loss of GFR was significantly and independently associated with lower risk of mortality and improved survival in dialysis patients.[13,14,16]
	• The CHOICE investigators showed that, in patients starting dialysis, preserved RRF at 1 year exhibited better survival rates, improved quality of life, less inflammation, and reduced erythropoietin use compared with those without RRF.[1,17]

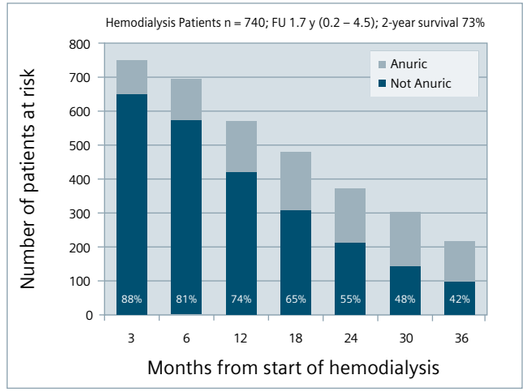


Figure 1. RRF in patients on hemodialysis (data from the NECOSAD study; adapted from Termorshuizen et al., 2004).[14]

These data reinforce the need for appropriate management strategies that may help to preserve RRF in dialysis patients. This is important not only because of the health-related benefits of RRF, but also because dialysis prescriptions can be individualized and dietary and fluid restrictions made less stringent in patients with higher RRF levels.[20–25] It is therefore essential to quantify the contribution of RRF to total solute clearance in patients on dialysis and to continually monitor patients over time.[1] These regular native kidney status updates enable treating physicians to provide optimal management and treatment strategies for their patients, which is why the most accurate (and routine-suited) measurements of RRF possible are required.[26]

Measurement of Residual Renal Function

Renal function may be assessed by direct GFR measurement by inulin or other GFR measurement techniques. However, these techniques are labor intensive and are not suitable for routine clinical use. Because of this, estimations of GFR (eGFR) via equations based on serum creatinine or cystatin C levels are the current guideline-recommended methods for monitoring patients with chronic kidney disease (CKD).[3,4,25,27–30] The European Best Practice Guidelines (EBPG) on dialysis strategies require that regular measurement of RRF be conducted in patients undergoing dialysis.[27,28] The EBPG for hemodialysis recommend that renal function be quantified as GFR—calculated from the mass of urea and creatinine in an interdialytic urine collection and from average concentrations of urea and creatinine in the blood[18]—while peritoneal dialysis guidelines specify that RRF may be quantified by urea clearance by calculating the mass of urea in urine (Table 2).[27,28]

Despite their common use in CKD, eGFR calculations based on urea or creatinine clearance may lack both precision and accuracy in patients undergoing renal replacement therapy and are not recommended nor validated for this patient population.[2,31,32] Since urea is reabsorbed by the renal tubules and creatinine is secreted by the renal tubules, it is thought that urea clearance may underestimate GFR by up to 40%, while creatinine measurements may overestimate GFR.[27,28] In addition, interdialytic urine collection (approximately 48 hours) can be cumbersome for patients and, consequently, can be an unreliable measure. As such, estimation of RRF in patients on dialysis continues to be problematic,[33] and there clearly remains an unmet need for an accurate and reliable endogenous biomarker for RRF that is simple to use in a clinical setting, similar to the use of serum creatinine estimated GFR (eGFR) in nondialysis patients.

Use of Low Molecular Weight Proteins to Assess RRF

As the kidneys show a high clearance of molecules over a wide range of molecular masses (up to 40 – 60 kDa),[26] small solutes such as creatinine and urea only partially reflect dialytic clearance. Because of this, low molecular weight proteins (LMWPs; 3 – 40 kDa) may better reflect clearance of uremic toxins.[26] Urea and creatinine are efficiently removed during dialysis; therefore, their concentrations in the blood are not in steady state, reflecting a combination of RRF and dialysis clearance. LMWPs are also freely filtered by the native kidney but, depending on size, may be less affected or not removed by dialysis and have therefore been proposed as useful tools for estimating RRF.[34]

LMWPs are cleared from the plasma through glomerular filtration, tubular resorption, and subsequent degradation in tubular cells. Therefore, barring additional influences on their production or clearance, a reduction in glomerular filtration correlates with increased LMWP serum concentrations.[34] The elimination of LMWPs during hemodialysis depends on protein size and specification of the dialysis membrane used (Figure 2).[26] Furthermore, in contrast to other markers such as serum creatinine, the plasma concentration of LMWPs such as cystatin C and beta-trace protein (BTP) does not appear to be affected by gender, diet, fitness, or body composition and so may represent a more accurate surrogate measurement of RRF than creatinine or urea.[34]

Table 2. Guideline recommendations for RRF determination in dialysis patients.[25,27–29]

Guideline	Recommendation for RRF Measurement
2007 European Best Practice Guidelines (EBPG) dialysis strategy[25,26]	Hemodialysis: • RRF may be taken into account for dialysis dose measurement, provided it is measured frequently enough to avoid overestimation (typically every 2 months) due to the natural decline of GFR over time. • Renal function may be quantified as GFR, calculated from the mass of urea and creatinine in an interdialytic urine collection and average concentrations of urea and creatinine in the blood during collection.
2006 Kidney Disease Outcomes Quality Initiative (KDOQI)[27,28]	Hemodialysis: • It is important to measure RRF frequently to avoid prolonged periods of inadequate dialysis due to the natural decline of RRF. • As the rate of loss varies among patients, monthly measurements are advised in most cases, whereas in others with good urine output, quarterly measurements are advised. • The preferred measure of RRF is urea clearance, differing from recommended measures of RRF in patients with CKD stages 1 to 4, for whom creatinine clearance has been the traditional index, as well as the serum creatinine-based estimate of GFR derived from the modification of diet in the MDRD renal disease study. • In patients with K_{urea} ≥2 mL/min/1.73 m^2, the minimum session $spKt/V_{urea}$ can be reduced. Peritoneal Dialysis: • RRF should be measured within the first month after initiation of dialysis and once every 4 months thereafter. • For patients with RRF of >100 mL/d urine output, 24-hour urine collection for volume and solute clearance determinations should be obtained at a minimum of every 2 months. • For patients with limited/no RRF (≤100 mL/d urine output), the minimum delivered dose of total small-solute clearance should be peritoneal Kt/V_{urea} of at least 1.7 per week, measured the first month after starting dialysis and at least once every 4 months thereafter.

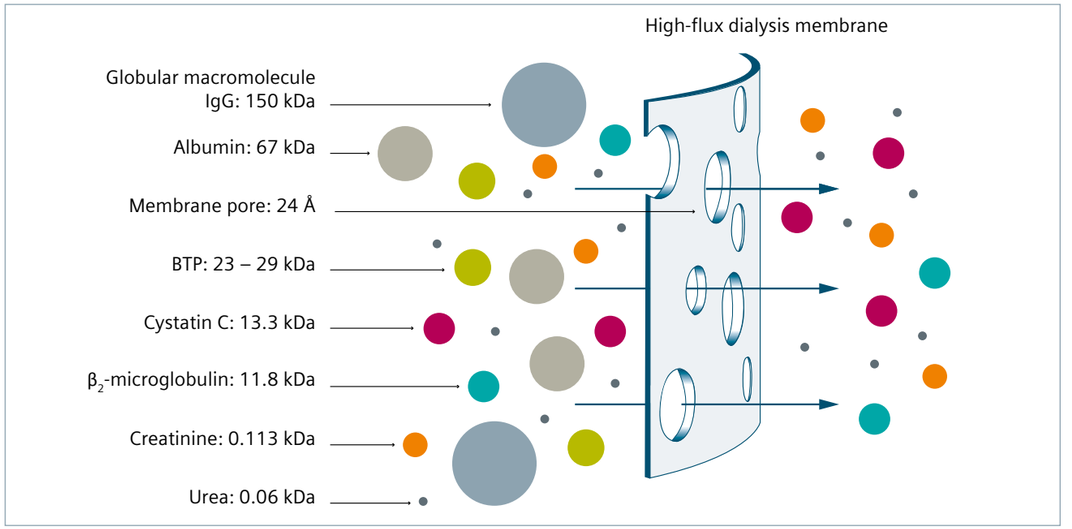


Figure 2. Marker molecule size vs. high-flux dialysis membrane pore diameter.[35,36]

BTP as a Measure of eGFR

One of the novel LMWPs identified as a potential tool for estimating renal function is BTP (also known as prostaglandin D_2 synthase), a 23 – 29 kDa serum LMWP that has traditionally been used as a marker of cerebrospinal fluid leakage.[37] There are two distinct types of prostaglandin D_2 synthases that have evolved from different protein families.[38] The first type of prostaglandin D_2 synthase belongs to the σ-class of glutathione S-transferases (requiring glutathione for its function), and the second is a glutathione-independent enzyme called lipocalin-type prostaglandin D_2 synthase, also known as BTP.[38] BTP is a dual-functioning protein, acting enzymatically within cells and as a lipophilic ligand-binding protein after it has been secreted by the cell.[38] The biological actions of BTP include vasodilation, bronchoconstriction, inhibition of platelet aggregation, and recruitment of inflammatory cells.[37] Like other LMWPs, BTP is freely filtered through the glomerulus and then completely reabsorbed by proximal tubule; therefore, the presence of BTP in the urine is thought to be indicative of tubular damage, while plasma or serum levels reflect GFR.[26,39,40]

Several studies have shown that serum BTP may be a sensitive endogenous marker of GFR.[1,2,41] Serum BTP levels, like cystatin C levels, increase as kidney function decreases,[1,2,41] and the development of formulae that may be used to translate measurements of serum BTP into eGFR have been devised for several patient populations.

Cystatin C has been increasingly implemented into routine clinical practice, and CKD guidelines and studies suggest that BTP is equivalent to cystatin C as a measure of eGFR.[2,25,30,34,42] Because of this, further studies on BTP have focused on patient populations in which cystatin C is of limited value, such as dialysis patients and transplant recipients (due to the influence of glucocorticoids on cystatin C levels).[41] White et al.[41] published an equation for eGFR using BTP derived from a cohort of 163 adult transplant recipients. Investigators used ^{99m}Tc-DTPA-measured GFR and stepwise multiple regression (variables: BTP, urea, sex, albumin, creatinine, age, and race)[41] to establish the following simple equation:

$eGFR = 112.1 \times BTP^{-0.662} \times urea^{-0.280} \times (0.880$ if the patient is female$)$[41]

(BTP: mg/L; urea: mmol/L; eGFR: mL/min/1.73 m^2)

A separate equation incorporating creatinine instead of urea was also developed in the event that urea measurements were unavailable.[41] Overall, both equations showed improved performance over the abbreviated MDRD equation at higher GFRs.[41] The findings of White et al.[41]

were supported by the study in renal transplant recipients conducted by Pöge et al.,[43] which confirmed that BTP-based eGFR calculations provide a reliable alternative to the MDRD equation in specific patient populations.[43]

BTP-based eGFR calculations have also been developed for use in pediatric patients. Benlamri et al.[37] measured GFR, serum creatinine, and BTP in 387 pediatric patients with various renal pathologies who underwent 474 ^{99m}Tc-DTPA renal scans with the aim of developing a BTP-based formula for calculating eGFR.[37] Using stepwise linear regression analysis validated with a separate control group, the following formula was developed:[37]

eGFR = 10^(1.902 + (0.9515xLOG(1/BTP)))

The BTP-based formula was found to estimate GFR in pediatric patients with adequate precision and provided significantly improved accuracy over the Schwartz formula (Figure 3).[37,44] The findings of these studies indicate that BTP is an accurate endogenous marker for GFR estimation in both adult and pediatric patient populations.[43,37,41,44,45]

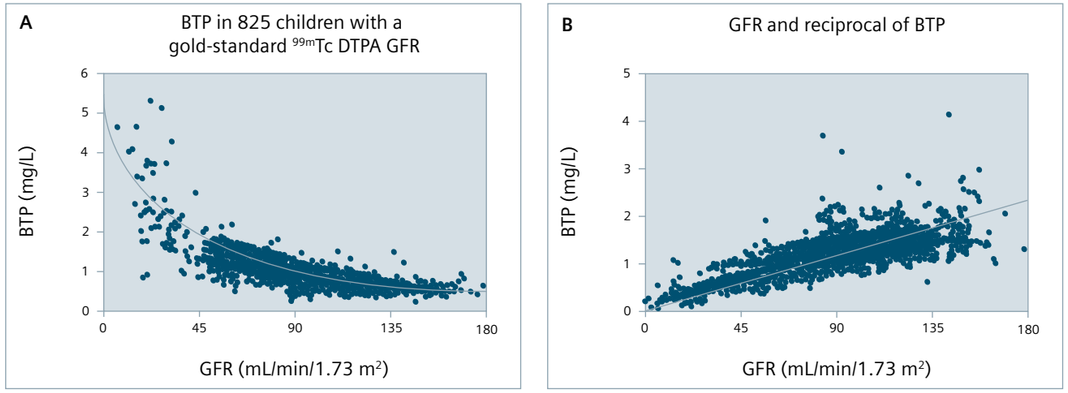


Figure 3. **(A)** The relationship between ^{99m}Tc-DTPA-measured GFR and BTP in 825 children with various stages of CKD. **(B)** The reciprocal relationship between ^{99m}Tc-DTPA-measured GFR and BTP in 825 children with various stages of CKD (adapted from Filler et al., 2014).[44]

BTP as a Marker of RRF

Although commonly used to assess GFR, LMWPs such as β_2-microglobulin (11.8 kDa) and cystatin C (13 kDa) are partially eliminated by conventional (high-flux) hemodialysis, hemodiafiltration, or hemofiltration (Figure 2).[26] The first study to investigate the influence of dialysis on LMWPs including BTP was published by Lindström et al. in 2008.[26] The study investigated the elimination patterns of LMWPs (β_2-microglobulin, cystatin C, and BTP) in plasma samples obtained pre- and post-dialysis from patients treated with low-flux hemodialysis (n = 17), post-dilution hemodiafiltration (n = 13), and pre-dilution hemofiltration (n = 8).[26] Conventional hemodialysis with low-flux membranes resulted in a high elimination of small molecules (urea and creatinine) but did not reduce the levels of the LMWPs (Figure 4).[26] With low-flux membranes, BTP elimination was found to be equivalent to the elimination rates for β_2-microglobulin and cystatin C, and the levels of these three LMWPs did not decrease following hemodialysis (Figure 4).[26] With the larger pore size, high-flux membranes allow a partial clearance of cystatin C, whereas BTP is not filtered at all.[26] High-flux membranes (with larger pores) are now routinely used for hemodialysis patients.

The study of Gerhardt et al. in 2008 showed that higher GFR was associated with lower levels of BTP but not serum creatinine in the pre-dialysis patient population and confirmed the observation that BTP is not cleared by dialysis in patients undergoing maintenance hemodialysis with high-flux dialyzers (Figure 5; Figure 6 A and B).[46] Hemodialysis did not significantly affect serum BTP levels (pre-treatment = 8.1 ±4.1 mg/L; post-treatment = 7.7 ±4.1 mg/L; Figure 5). In contrast, β_2-microglobulin decreased by 50 – 70% with high-flux membranes.[46] Hemodiafiltration did reduce BTP levels in some patients (n = 6/21), but the resulting decrease in serum concentration was small (Figure 5).[46] These results suggest that serum BTP is a potentially useful and accurate marker of renal function in dialysis patients as it is not significantly affected by the dialysis procedure.[26,46]

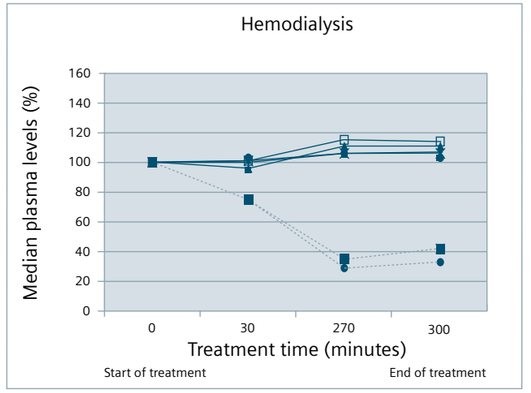


Figure 4. The resulting median levels of the measured RRF markers at different time-points during hemodialysis expressed as percentages of the original levels; cystatin C (♦), BTP (□), β_2-microglobulin (x), creatinine (■), and urea (○) (adapted from Lindström et al., 2008).[26]

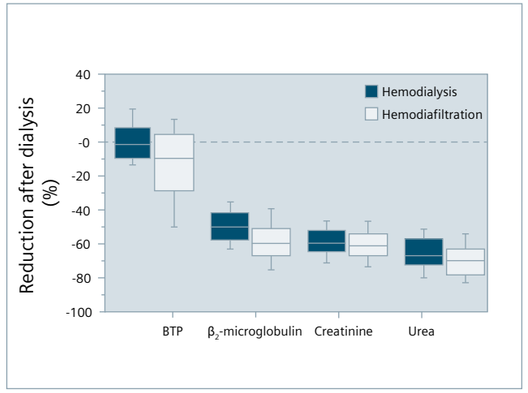


Figure 5. Pre- and post-hemodialysis levels of markers of GFR and RRF (adapted from Gerhardt et al., 2008).[46]

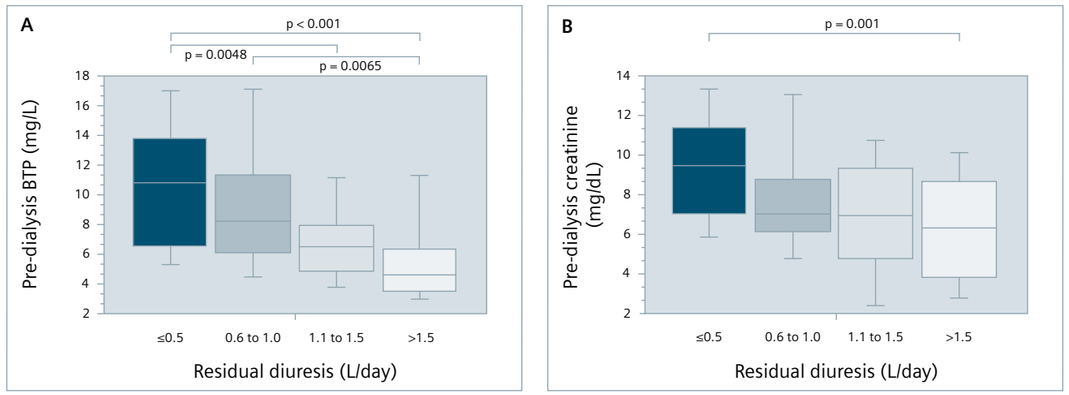
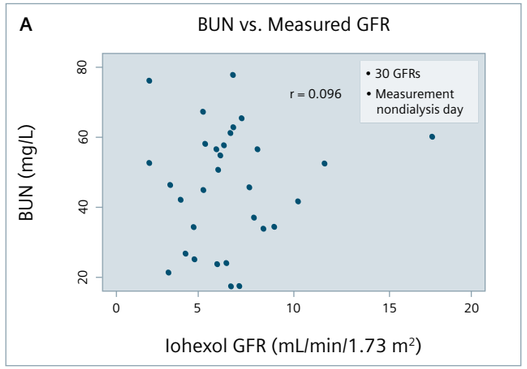
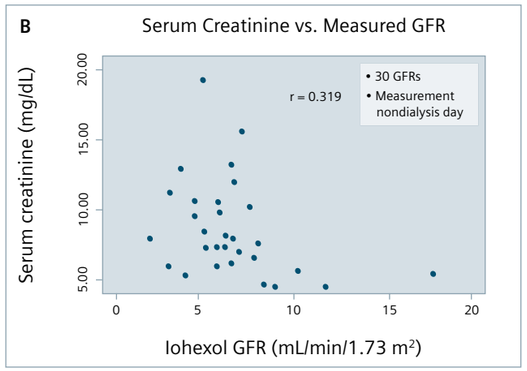


Figure 6. **(A)** Pre-dialysis levels of BTP in dialysis patients with differing levels of RRF. **(B)** Pre-dialysis levels of serum creatinine in dialysis patients with differing levels of RRF (adapted from Gerhardt et al., 2008).[46]





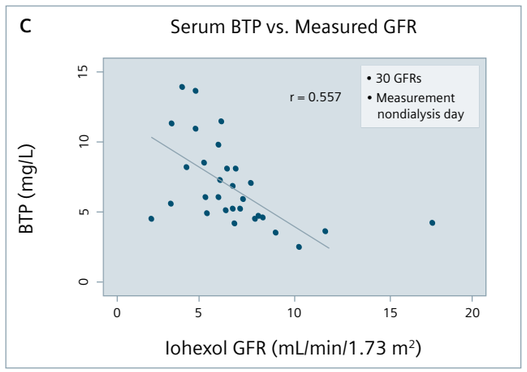


Figure 7. **(A)** Correlation between measured GFR and BUN in 30 patients undergoing dialysis. **(B)** Correlation between measured GFR and serum creatinine in 30 patients undergoing dialysis. **(C)** Correlation between measured GFR and serum BTP in 30 patients undergoing dialysis (adapted from Shafi, IFCC Congress Milano, 2013).[47]

Findings in dialysis patients presented in 2013 at the International Federation of Clinical Chemistry (IFCC) and Laboratory Medicine Congress demonstrated that, while there is no significant correlation between blood urea nitrogen (BUN) or serum creatinine and measured GFR, there is a significant correlation between BTP and measured GFR (r = 0.096 for BUN, r = 0.319 for serum creatinine, and r = 0.557 for BTP; Figures 7 A – C).[47] Additional findings were also presented at the American Society of Nephrology in November 2014. These data further support the use of BTP as a marker for RRF.

BTP and Risk Prediction

Kidney disease is a well-established risk factor for cardiovascular disease and all-cause mortality. Several studies have shown such an association for serum BTP as well.[1,2,42,48] Like cystatin C, but unlike serum creatinine (in patients not on dialysis), BTP is a significant risk predictor for all-cause and cardiovascular mortality, and the strong association with risk is also seen at normal GFR range (>60 mL/min/1.73 m²).[1,48] BTP has also been shown to be a better predictor of ESRD than cystatin C and serum creatinine.[42]

In a study by Shafi et al.,[1] the investigators evaluated serum BTP levels in baseline samples from 503 participants from the CHOICE study cohort of incident dialysis patients. They found that serum BTP levels were higher in patients with no urine output compared with those with urine output (9.0 ±3.5 vs. 7.6 ±3.1 mg/L; p < 0.001; Figure 8),[1] indicating that BTP levels increase as RRF declines. Importantly, the CHOICE study[1] demonstrated that serum BTP level is an independent predictor of death and cardiovascular mortality in incident hemodialysis patients (Figure 9).[1]

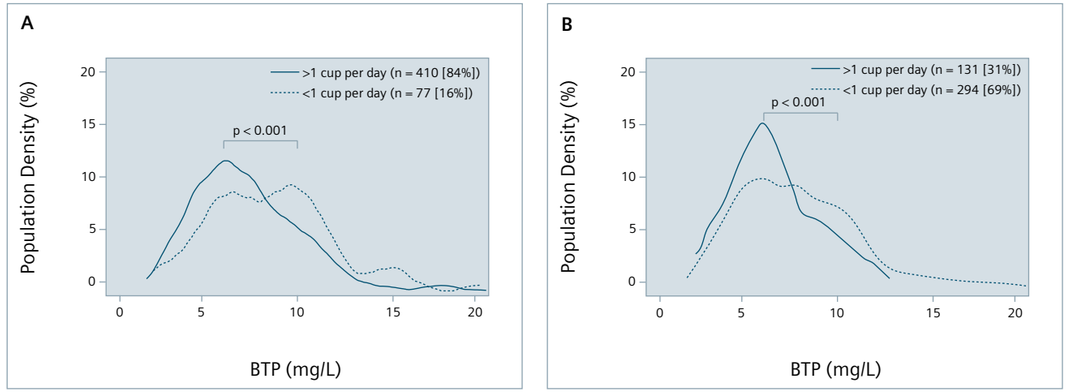


Figure 8. Serum BTP and self-reported urine output at **(A)** baseline and **(B)** 1-year follow-up (adapted from Shafi et al., 2012).[1]

Findings from the CHOICE study have been supported by the outcomes of investigations by Foster et al.,[48] who identified increased BTP levels as a predictor of all-cause and cardiovascular mortality in adults in the United States.[48] This significant association with risk prediction was also observed in patients with higher eGFR (eGFR >60 mL/min/1.73 m²).[48] It has also been shown that, like cystatin C, BTP is a reliable predictor of common comorbidities associated with renal impairment, such as cardiovascular disease and the development of ESRD.[2,42] The results of these studies support the use of BTP as an alternative or additional marker to traditional risk prediction.[48]

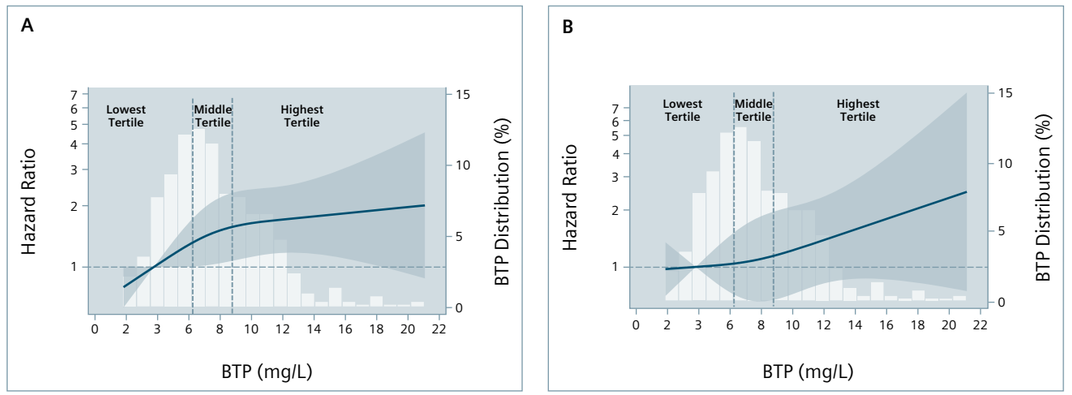


Figure 9. Serum BTP and adjusted risk of **(A)** all-cause and **(B)** cardiovascular mortality (adapted from Shafi et al., 2012).[1]

Summary

The EBPG[27,28] for hemodialysis require that regular measurement of RRF be conducted in patients undergoing dialysis. This is important, as higher levels of RRF are associated with improved survival and contribute significantly to the overall health and well-being of dialysis patients, as well as informing treatment decisions.[19,20] Due to the inaccuracy of conventional eGFR biomarkers during dialysis (such as cystatin C and serum creatinine), there is currently no simple method for eGFR assessment in dialysis patients.[1] Serum BTP has emerged as a reliable endogenous biomarker to address this unmet need, as its concentration is not significantly affected by dialysis, and it is strongly associated with RRF.[46] As such, BTP may serve as a dependable, replicable method for eGFR assessment and as an endogenous marker of RRF in patients undergoing dialysis.[46]

The evidence presented suggests that a simple blood test for BTP would serve to provide a reliable estimation of RRF, allowing accurate estimates of endogenous renal contribution to clearance without the need for cumbersome urine collection and other complex procedures (GFR measurement). Furthermore, these improvements in accuracy for RRF measurements would allow physicians to have more confidence when adjusting the dose and frequency of dialysis and to proactively anticipate and manage complications in order to maintain RRF in their patients.

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