Special Article

Current status of chronic kidney disease biomarkers among Thai patients

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Abstract

Patients with chronic kidney disease (CKD) have a higher risk of mortality, mostly from cardiovascular complications. Currently, the biomarkers for diagnosis and monitoring of CKD are albuminuria, serum creatinine, estimated glomerular filtration rate, and kidney biopsy which have several limitations such as the sensitivity of the test and the invasiveness of the procedure, respectively. Recent developments have identified a number of novel biomarkers in serum or urine that can determine the potential risk of kidney damage, distinguish different types of renal injury, predict the progression of disease and have the potential to assess the efficacy of therapeutic intervention. Novel biomarkers of the processes that induce progressive loss in renal function may ultimately prove to be better predictors of renal progression and prognosis in CKD. In this article, we focus on the potential applications of these biomarkers in Thai CKD.

Keywords: tubulointerstitial damage, chronic kidney disease, biomarkers

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According to the Thailand Renal Replacement Therapy (TRRT) Registry Report 2014, the common causes of end stage renal disease (ESRD) are diabetes mellitus, hypertension, chronic tubulointerstitial disease and chronic glomerulonephritis. The common causes of chronic glomerulonephritis in Thailand include IgA nephropathy and lupus nephritis. In addition, chronic kidney disease (CKD) after kidney transplantation is the only CKD that we know the real onset of the disease and the samples collection can be easily completed. With the increasing prevalence of kidney transplantation patients in Thailand, then CKD in kidney transplantation will be another interesting CKD group.

CKD is a progressive loss in renal function over a period of months or years resulted from the adaptation of abnormal kidney function both quantitatively and qualitatively. CKD is currently identified by the albuminuria and/or the higher levels of creatinine, indicate a lower glomerular filtration rate (GFR) resulting in waste products accumulation and clinical symptoms. Creatinine levels may be normal in the early stages of CKD, and the condition is discovered if urinalysis shows that the kidney is allowing the loss of protein or red blood cells into the urine. To fully investigate the underlying cause of kidney damage, various forms of medical imaging, blood tests and often renal biopsy are employed to find out if there is a reversible cause for the kidney malfunction. The various types of CKD have different etiologies, which causes the initial injury by incompletely-understood disease-specific immunological and metabolic mechanisms. These events affect individual components of the kidney and provoke inflammation to varying degrees in different diseases. Despite different etiologies, the various types of CKD share common pathogenic mechanisms that culminate in progressive renal fibrosis due to extracellular matrix deposition and tubular atrophy leading to irreversible loss of renal function. These processes involve diverse cell types including native renal cells and infiltrating leucocytes, different mediators both promoting and antagonizing disease progression and cross-talk between glomerular and tubulointerstitial compartments.

Recent developments have identified a number of novel biomarkers in serum or urine that can determine the potential risk of kidney damage, distinguish different types of renal injury, predict the progression of disease and have the potential to assess the efficacy of therapeutic intervention. Some of these biomarkers can be used independently while others are more beneficial when used in combination with knowledge of other clinical risk factors. Advances in gene expression analysis, chromatography, mass spectrometry and the development of sensitive enzyme-linked immunosorbent assays have facilitated accurate quantification of many biomarkers. This article focuses on describing new and established biomarkers, which identify and measure the various pathophysiological processes that promote Thai CKD. It provides the different classes of renal biomarkers that can be assessed in serum/plasma and urine, including markers of renal function, cellular injury, immune responses and fibrosis. However, it does explore the current status of these biomarkers in terms of their multicenter clinical validation.

Currently, the biomarkers for diagnosis and monitoring of CKD are albuminuria, serum creatinine and kidney biopsy which have several limitations such as the sensitivity of the test and the invasiveness of the procedure, respectively. On the other hand, the management of CKD in different underlying diseases will be useful for the clinicians. For examples, the CKD in kidney transplantation will lead to the avoidance of calcineurin inhibitors or CKD in lupus nephritis might be useful for the reduction of immunosuppressive drugs. Then the better biomarkers for CKD are in urgently needed.

Potential biomarkers for overall Thai CKD population

1. Cystatin C

Serum cystatin C is an established novel biomarker of GFR that is slightly more sensitive than serum creatinine in detecting moderate reductions in GFR. However, serum cystatin C is less well-studied in the follow up of CKD progression and there is limited data correlating cystatin C with renal histological parameters. Our cross-sectional study was performed in chronic glomerulonephritis patients. CKD-EPI-creatinine-cystatin C equation estimated GFR with little bias, and the highest accuracy among patients with chronic glomerulonephritis. This equation gave a better estimate of GFR that the equation based on serum creatinine.[1]

Based on a Thai worker cohort data (EGAT), we found that CKD stage 3-5 classified using either serum cystatin C or combined cystatin C and creatinine CKD-EPI estimated GFR equations had increased all cause and cardiovascular mortality, cardiovascular events and coronary heart disease compared to no CKD after 18 years follow-up.(manuscript in preparation) After adjustments for traditional cardiovascular risk factors, subjects with CKD stage 3b-5 by cystatin c or combined CKD-EPI equations had increased all cause or cardiovascular mortality compared to subjects with no CKD. The net reclassification index for each stage CKD for prediction of all-cause mortality and cardiovascular events was better using CKD-EPI equations based on cystatin C compared to creatinine.

Using the same worker cohort, we found that among subjects with preserved GFR (estimated GFR >60 mL/min/1.73 m^2 by creatinine based CKD-EPI equation), those with estimated GFR <60 mL/min/1.73 m^2 based on CKD-EPI cystatin C equation had significantly increased risk for new reduced GFR (estimated GFR creatinine CKD-EPI <60 mL/min/1.73 m^2) at 15 years follow-up even after adjusting for traditional factors. (manuscript in preparation)

Therefore, serum cystatin C based CKD-EPI GFR equations can predict mortality, cardiovascular outcomes and new onset decreased GFR in Thai community based subjects and appear to be useful in chronic glomerulonephritis. Further studies are necessary to fully evaluate the cost-benefit of cystatin C measurement in different subgroups.

2. Neutrophil-gelatinase associated lipocalin (NGAL)

NGAL is a promising biomarker of acute kidney injury (AKI). In CKD, there is a growing literature suggesting that NGAL is also a marker of kidney disease and severity. In Thai subjects with lupus nephritis[2], diabetic nephropathy[3], primary glomerulonephritis[4], nondiabetic glomerular diseases with proteinuria[5] and kidney transplant recipients, urine NGAL concentrations were associated with renal damage markers. We performed a diagnostic and prospective multi-center study in lupus nephritis patients. Urine NGAL at baseline is better performance than conventional markers for predicting a clinical response to treatment of active lupus nephritis.[2] It also was postulated that the rise in NGAL may not just be due to the decreased renal clearance, but could be due to production from the inflamed tubular cells, compared with a rise in serum creatinine or a drop in GFR, which are due to loss of nephrons. In addition to serum cystatin C and urine NGAL, we propose to study several other biomarkers in specific kidney diseases. Most of these other biomarkers have been identified in small groups of patients with specific diseases, but remain to be tested in larger groups of patients with different diseases or compared to other novel biomarkers. The choice of the marker to test in a given disease will depend on previous experimental data and clinical data.

Potential biomarkers for diabetic nephropathy

Many of the discovered biomarkers for diabetic nephropathy were identified by transcriptomic and proteomic analyses of renal tissues after injury. As such, there tends to be a bias toward identifying markers from the renal tubulointerstitium, reflecting its greater mass compared with the vascular and glomerular compartments. Recently, certain biomarkers, which were initially identified in AKI, also have been reported to confer value in the evaluation of patients with CKD. Urinary biomarkers such as cystatin C, kidney injury molecule-1 (KIM-1), NGAL, angiotensinogen, periostin and monocyte chemoattractant protein-1 (MCP-1) reflect tubular injury (Figure 1).

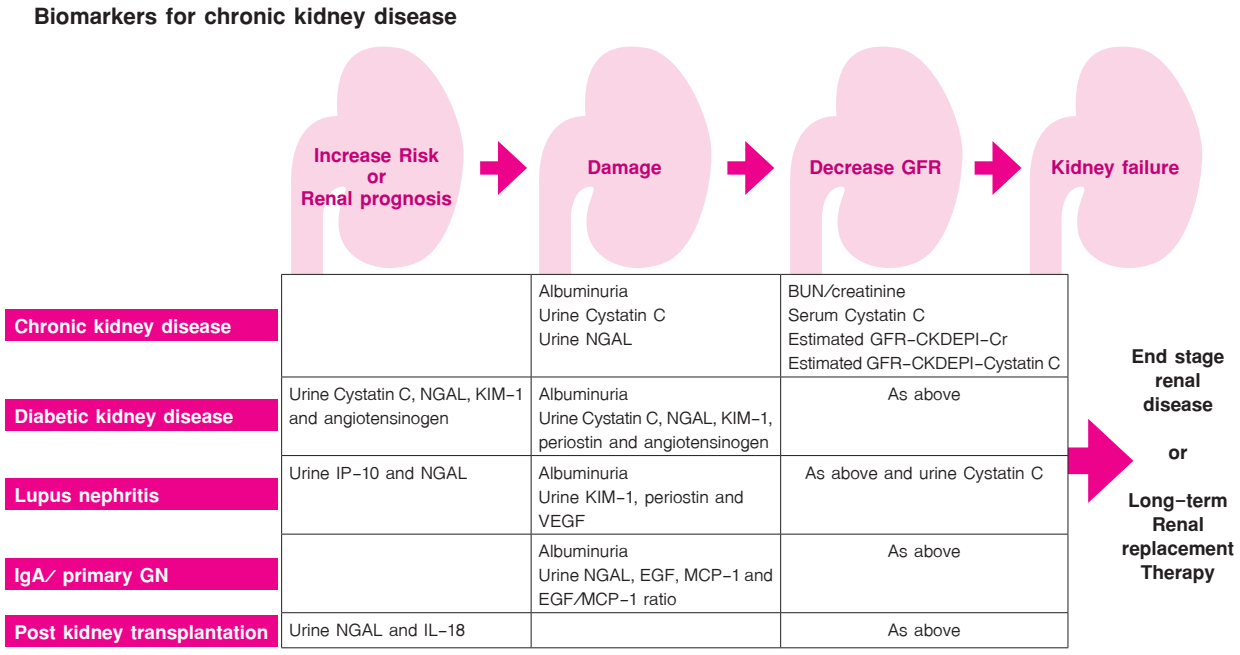

Figure 1 Potential biomarkers for CKD patients

1. **Cystatin-C** has a molecular weight of 13 kDa, is easily filtered by the glomeruli and is reabsorbed and catabolized by the proximal tubule. From a prospective observational study, urine cystatin C predicted the progression of type 2 diabetes with nephropathy.[6] Our research found that type 2 diabetes (T2DM) with rapid renal progression had significantly increased levels of urine cystatin C when compared with the nonrapid renal progression group.[3] Finally, urine cystatin C was an independent predictor of CKD progression in T2DM.

2. **NGAL** is expressed in the renal tubular epithelium, and a rise in urinary concentrations may provide an indication of acute renal injury that is detectable before the rise in serum creatinine concentration. In a related study carried out among patients with diabetic nephropathy, elevated urine NGAL level was reported to be associated with the progressive course of the disease leading to ESRD.[7] Similarly, in observational follow-up and our cohort study in T2DM patients, high urine NGAL levels at baseline correlated with rapid decline of estimated GFR levels and increased serum creatinine.[3,7]

3. **KIM-1** is a type 1 membrane protein expressed on the apical membrane of proximal tubule cells and it is associated with tubulointerstitial inflammation in patients with proteinuric nephropathy, including diabetic nephropathy.[8] From a cross-sectional descriptive study; urine KIM-1 increased in type 2 diabetes with normoalbuminuria and mildly increased albuminuria.[9] Moreover, our study confirmed that urine KIM-1 predicted the rapid decline of GFR[3], and urine KIM-1 levels were significantly higher in the patients who progressed from macro-albuminuria to late stage CKD.[10]

4. **Angiotensinogen** is the only known substrate for renin. Renal angiotensinogen is formed primarily in proximal tubular cells and is secreted in the tubular fluid. The activated intrarenal RAS was recently proposed to be involved in the progression of renal injury in multiple models of hypertension and in kidney diseases. Urinary angiotensinogen level also correlates with intrarenal angiotensinogen levels and we confirmed that urine angiotensinogen is independently associated with albuminuria and rapid GFR decline in T2DM.[3,11] In diabetes with normo-albuminuria, urinary angiotensinogen was higher than in controls and it demonstrated good performance in differentiating each stage of T2DM from controls.[12]

5. **Periostin** is involved in the fibrosis process and

tissue remodeling, kidney development and tubular dedifferentiation in experimental models. Our study describes, for the first time, the renal expression and urinary excretion of periostin in rats after CKD and in the kidney of mice with diabetes.[13] It serves as a marker of renal tubular injury and is also correlated with worsening renal outcomes including serum creatinine, blood urea nitrogen and estimated GFR in various chronic progressive kidney injury.[14] Urinary periostin levels were more significantly elevated among patients of normo-albuminuria, micro-albuminuria and macro-albuminuria compared with levels of healthy controls. Increased urine periostin level was significantly correlated with aging, high albuminuria and decline of GFR.[15]

6. MCP-1 as members of the CC chemokine family are a major factor influencing macrophage accumulation in both animal and human models of renal damage. MCP-1 is upregulated and expressed in the diabetic glomerular and renal tubular epithelium, and a rise in urinary MCP-1 levels correlated with the extent of interstitial inflammatory infiltrate.[16] In contrast, epidermal growth factor (EGF), a peptide growth factor, plays a protective role in progressive renal injury. EGF plays an important role in restoring barrier function in the healing phase of renal injury and is also a critical in vivo renal cell survival factor for developmentally mature kidneys.[17] Urinary levels of EGF and EGF/MCP-1 ratios are inversely correlated with the extent of tubulointerstitial damage and determined renal prognosis in glomerulonephritis.[18] Our initial analysis found that urinary MCP-1 levels and EGF/MCP-1 ratios were independently associated renal progression among T2DM patients.

Potential biomarkers for IgA nephropathy and chronic glomerulonephritis

The pathogenesis of IgA nephropathy is not clear, though it is likely that an aberrant glycosylation pattern of IgA is involved.[19] The Oxford classification of IgA nephropathy identified five types of histological lesions (known as the MESTC score) associated with the development of ESRD and/or a 50 % reduction in estimated GFR. Recently, biomarkers in serum (galactose-deficient IgA1, IgA/IgG autoantibodies against galactose-deficient IgA1, and soluble CD 89-IgA complexes) and urine (e.g. MCP-1, EGF, soluble transferrin receptor, fractalkine, laminin G-like 3 peptide, κ light chains, and mannan-binding lectin) have been identified. We have evaluated the following:

Renal pathological markers

1. Oxford score We evaluated the predictive effects of the 2017 Revised Oxford Score on ESRD and 50% loss of GFR in Thai patients with IgA nephropathy in their native kidneys. We found that segmental sclerosis, tubulointerstitial lesions T1 and T2 increased the risk of renal outcome by multivariate analysis. C score was not significant in our study.

We also evaluated the predictive effects of the 2017 Revised Oxford Score on ESRD and 50% loss of GFR in Thai patients with recurrent IgA nephropathy in kidney transplantation. Similarly, we found that tubulointerstitial lesions T1 and T2 increased the risk of renal outcome by multivariate analysis.

It is possible that many of Thai patients with IgA nephropathy in both native and transplant kidneys present late to kidney in the course of disease rendering tubulointerstitial scores to become more important. The roles of glomerular features may be more important if patients are biopsied earlier, but this remains to be clarified in Thai subjects.

2. C4d staining Complement activation is increasingly recognized to have an important role in IgA nephropathy pathogenesis. We also evaluated the role of C4d staining in prognosis of IgA nephropathy. We found that C4d was a strong independent predictor of ESRD and 50% GFR decline. Future studies are necessary to confirm the role of C4d staining in the context of treatment.

Urine biomarkers

1. NGAL Since the tubulointersitium is critical to the development of ESRD, we explored the relationship of NGAL with severity of tubulointersitial disease with NGAL in IgA nephropathy and other primary glomerulonephritis such as focal segmental glomerulosclerosis (FSGS), membranous nephropathy and minimal change disease. We found that urine NGAL excretion to be predictive of moderate to severe tubulointerstitial fibrosis independent of estimated GFR and proteinuria.

In the second phase, we measured urine NGAL in patients with proteinuric primary glomerulonephritis including IgA nephropathy before and after treatment. We found that, urine NGAL/Cr correlated more strongly with proteinuria than with GFR at baseline. Changes in proteinuria after therapy correlate with changes in NGAL. Complete remission leads to lowering of NGAL/Cr to levels similar to normal subjects.

Our findings imply that proteinuria could confound the ability of NGAL to relate to renal histology and outcome predictions in primary glomerulonephritis. More studies are needed to determine if baseline and repeated NGAL measurements provide additional prognostic benefit in addition to conventional markers in primary glomerulonephritis.

2. EGF and MCP-1 MCP-1 is a potent chemokine that promotes the recruitment of inflammatory cells into the kidney and the release of several mediators including transforming

growth factor-beta. On the other hand, EGF, a peptide growth factor locally produced by the tubules may have protective roles. Decreased EGF has been found to be a strong predictor of tubulointerstitial damage in a wide variety of CKD using a transcriptomic driven approach.[20] Earlier, increased EGF/MCP-1 has been shown to correlate with adverse outcome of IgA nephropathy.[21] We evaluated the relationship of urinary EGF, MCP-1 and EGF/MCP-1 ratio in primary glomerulonephritis. We found that urinary EGF correlated with baseline estimated GFR and severity of tubulointerstitial fibrosis, but not with proteinuria.[18] In a follow-up study, urine EGF at the time of biopsy predicted complete response to treatment independent of conventional risk factors and correlated with estimated GFR at 2 years. (*Chanrat et al. Manuscript under review*) EGF/MCP-1 did not offer additional predictive advantage to EGF alone both for tubulointerstitial fibrosis or outcome.

Our data suggests that EGF might be a good predictor of tubulointerstitial fibrosis and response to therapy which is not influenced by systemic production or increased glomerular permeability. Larger studies are necessary to determine full potential of EGF in treatment of primary glomerulonephritis.

Serum biomarkers

Recently, several biomarkers have been proposed as being diagnostic or prognostic in specific types of glomerulonephritis. The M-type phospholipase A2 receptor 1 (PLA2R) represents the major target antigen in primary membranous nephropathy, and thrombospondin type 1 domain-containing 7A (THSD7A) was more recently identified as a minor antigen. Serological tests for anti-PLA2R as well as kidney biopsy specimen staining for PLA2R exhibit more than 90% specificity and 70% to 80% sensitivity for the diagnosis of primary MN in most populations. The assays distinguish most cases of primary membranous nephropathy from membranous nephropathy associated with other systemic diseases, and sequential titers of anti-PLA2R are useful to monitor treatment response.[22] In IgA nephropathy, some researchers have reported that the level of Gd-IgA1 in the sera of patients with IgA nephropathy is associated with disease progression, but this has not been consistently reported.[19] A recent meta-analysis suggests that the level of Gd-IgA1 in the serum or supernatant of cultured cells from peripheral blood or tonsils may be a useful biomarker for predicting IgA nephropathy, though the level of Gd-IgA1 was not significantly associated with disease severity.[23] Circulating factors have also been regarded as an important factor in the pathogenesis of FSGS. Soluble urokinase-type plasminogen activator receptor (suPAR) is a soluble form of uPAR, which is a membrane-bound protein in podocytes. It has recently been suggested as a potential circulating factor in FSGS. However, more recent studies have cast doubt on the specificity or the validity of this as a specific marker for FSGS.[24]

At present, antibody to PLA2R could be considered for diagnosis or monitoring of primary membranous nephropathy. The roles of serologic monitoring for membranous nephropathy or other glomerulonephritis requires further studies in Thai subjects.

Potential biomarkers for lupus nephritis

Lupus nephritis is among the top priority of kidney diseases which require non-invasive biomarker to detect active disease. The disease has broad range of renal manifestation from asymptomatic urine abnormality to rapidly progressive glomerulonephritis. The clinical manifestations depend on the type of renal pathology. Class IV lupus nephritis can become ESRD within months, whereas class V lupus nephritis shows nephrotic proteinuria with normal kidney function. Although, kidney biopsy is crucial for diagnosis and confirmation of relapse, it is not practical to repeat the procedure. For monitoring the disease activity, non-invasive test is needed.

Non-invasive tests for lupus nephritis

Current use of biomarkers for lupus nephritis are serum levels of the complement and anti-dsDNA. Although anti-dsDNA is specific for lupus nephritis, but it is useless in monitoring the activity of the disease. Elevated levels of serum creatinine and the presence of proteinuria are common manifestations of lupus nephritis. However, both markers are not specific nor early enough to diagnose active lupus nephritis. We reported that urine messenger RNA levels of cytokines may be useful for early diagnosis of class IV lupus nephritis as well as predicting response to initial treatment.[25] These cytokines include Th-1 related and growth factors (Figure 1). Interferon-inducible protein-10 (IP-10) shows the highest accuracy for diagnosis of active lupus nephritis. A prospective clinical trial is going to determine whether urine IP-10 levels can guide an initial treatment and avoid repeated kidney biopsy in known case of lupus nephritis. An interim result showed an advantage of this approach over the conventional approach. In clinical practice, patients often deny repeated kidney biopsies and sometimes have contra-indications such as bleeding diathesis. Urine cytokines can become useful indicators for beginning potent immunosuppressive drugs.

Future development of biomarkers for lupus nephritis is in progress. We performed multi-center study for biomarkers for lupus nephritis. We found two early biomarkers in multi-center study (Figure 1). Elevated levels of NGAL are detected in active lupus nephritis especially among non-responders. The other biomarker, IP-10, has been validated in a prospective study and should be added into

the clinical practice guideline. Easy and simple test of urine cytokines should be available at local hospitals so general practice doctors can take care of the patients first.

Different applications of the biomarkers

Figure 1 demonstrates many applications of novel biomarkers in lupus nephritis. Urine cytokines can be detected before the clinical and laboratory changes. Therefore, monitoring urine cytokine such as IP-10 should be useful at the lupus clinic. Another application of the biomarkers is to predict kidney pathology of severe lupus nephritis class IV.[26] In addition, urine cytokines can be used to predict renal pathology. Furthermore, we may use biomarkers to predict response to treatment and progression to CKD.[27]

Potential biomarkers for kidney transplant recipients

Post kidney transplantation is one of the important risk factor for CKD progression in the transplanted kidney, even with the post-operative normal renal function, due to several impacts. Perioperative ischemia, alloimmune responses, calcineurin inhibitor (CNI) nephrotoxicity and infections are the frequent events that initiate post transplanted-renal injury. And persistent and/or severe renal injury might lead to renal fibrosis as known as "interstitial fibrosis and tubular atrophy (IFTA)". Hence, the biomarkers for the prediction of post-transplanted CKD could be divided into, at least, 3 groups; i) the biomarkers indicating the ongoing insults [renal ischemia, immune activation, CNI monitoring (protocol biopsy) and infection (eg. chronic bacterial cystitis, BK nephropathy and cytomegalovirus infection), ii) the biomarker of renal injury (eg. serum creatinine, cystatin C, and NGAL) and iii) the markers of fibrosis production (eg. urine collagen) which, unfortunately, is still a work in progress

In the current clinical practice, estimated GFR, serum creatinine and protocol biopsy is the important procedures for IFTA surveillance. However, there are several questions and limitations, for example, does the recommended CNI level is too high for Thai population? and what is the less invasive IFTA biomarker than the protocol biopsy? We found increased urine cytokine (IL-18) along with increased urine NGAL from the baseline (but not absolute value of NGAL) in most of the patients in post-kidney transplantation group with increased dose of tacrolimus, even with normal serum creatinine. The delta change of urine NGAL during 3 months post-kidney transplantation could be used for the prediction of IFTA at 1 year post-KT (manuscript in revision). It is possible that CNI monitoring with urine NGAL measurement might be helpful for patients with kidney transplantation. In addition, we also explored urine exosome in kidney transplantation. Unfortunately, the urine volume that necessary for urine exosome extraction was very high to produce the consistent yield. Further studies are needed in both issues.

Conclusion

Novel biomarkers including cystatin C, NGAL and others may ultimately prove to be better predictors of renal progression, renal remission and prognosis in CKD patients. Our research integrated novel tubular biomarkers at the same time, and compared the performance of each tubular biomarker with standard urine albumin. This suggests that some novel biomarkers in figure 1 would not be simple surrogate indexes of baseline estimated GFR, but markers on their own, predicting CKD progression beyond the information provided by serum creatinine and other conventional risk factors.

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Conflict of Interests

The authors declare that no potential conflict of interests exists.

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