

## TOPICAL REVIEW

## Cardiac biomarkers and chronic renal diseases

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**Abstract:** Accelerated atherosclerosis can lead to an increased prevalence of coronary artery disease, heart failure, brain stroke and peripheral arterial disease. Thus, subjects with chronic renal failure are exposed to increased morbidity and mortality from cardiovascular events. A strong and pervasive link exists between kidney failure and cardiac disease. A variety of individual biomarkers have been evaluated and several have been found to successfully predict the outcome in patients with kidney disease. These include markers of myocardial necrosis, such as cardiac troponin T and I, markers of heart failure, such as B-type of natriuretic peptide and its associated inactive N-terminal fragment, markers of systemic inflammation – C-reactive protein, and an endogenous inhibitor of nitric oxide synthase—asymmetric dimethyl arginin.

Increased concentrations of C-reactive protein, B-type of natriuretic peptide, asymmetric dimethyl arginine, and troponin predict a high risk of cardiovascular mortality as well as a mortality due to other causes in patients with chronic renal failure or end stage renal disease (Tab. 1, Ref. 33). Full Text (Free, PDF) [www.bmj.sk](http://www.bmj.sk).  
Key words: cardiac biomarkers, chronic kidney diseases, chronic renal failure, end stage renal disease.

**Biomarkers and progression of kidney diseases**

Biomarkers are substances found in biological samples, such as blood and urine. They may reflect the presence of some disease or organ damage. Biomarkers are often used for diagnostic purposes; they can assess the prognosis or the effect of treatment. Biomarkers can be useful when comparing cardiovascular burden in a diverse population.

During last 10 years it has been proved that a moderate renal insufficiency (GF60 ml/min) is a very frequent finding in general population (1). Like coronary heart disease, chronic kidney disease (CKD) is related to several risk factors, including metabolic syndrome (hypertension, abdominal obesity, hypertriglyceridemia, fasting hyperglycemia, and low HDL) (2). However, these risk factors are not fully responsible for renal function loss. According to MDRD study (Modification of Diet in Renal Disease, 1997) these factors explained only 34 % of the variance of renal disease progression (3). So, there are unknown factors, which play an important role in reducing renal function in these patients. These factors are so called “biomarkers.”

In the recent years many studies have been performed and proved an important role of biomarkers: C-reactive protein (CRP), homocysteine, B-type of natriuretic peptide (BNP), troponin and asymmetrical dimethyl arginin (ADMA).

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**C-reactive protein**

Inflammation, a very important component of the pathogenesis of atherosclerosis, is an invasive sign in patients with chronic renal failure (CRF) or end stage renal disease (ESRD), respectively. Increased level of CRP is proved in 70 % of patients on chronic dialysis (4). CRP is increased frequently in patients with metabolic syndrome. This fact is referred to the release of IL-6 (interleukin 6), TNF- $\alpha$  (tumor necrosis factor-alpha) and other cytokines by the adipose tissue. Systemic inflammation in obese and overweight subjects may affect both the cardiovascular system and kidneys (1).

Outcomes of epidemiological studies support the idea that inflammation plays an important role in renal dysfunction (1).

The relationship between inflammation and renal function in patients with progressive renal disease has been minimally investigated. Two small studies showed an inverse relation between CRP and IL-6 to creatinine clearance (5, 6).

Tonelli, in a group of patients with myocardial infarction and a mild CRF, demonstrated that the loss of renal function is inversely related to CRP (7). Moreover, this study proved that statin treatment significantly reduced the progression of renal disease. There is the evidence that an increased plasma CRP is an early marker of renal dysfunction. In addition, CRP is one of the strongest markers of cardiovascular risk in patients with chronic renal insufficiency.

According to Tripepi, IL-6 and fibrinogen are stronger predictors of cardiovascular and all cause mortality compared to CRP. As it is reliable and well standardized, it remains a favorite between other markers, as a potential candidate for risk stratification in subjects with CRF or ESRD, respectively (8).

Chronic kidney disease (CKD) is very frequent (in 80–90 %) in patients with coronary heart disease (or in persons with risk of coronary heart disease). CRP could be very useful to guide the treatment in these patients. Its measurement could be recommended in subjects with chronic kidney disease and especially in patients with coronary heart disease (9).

### Homocysteine

Plasma homocysteine level is increased in patients with reduced renal function. Hyperhomocysteinemia can alter renal hemodynamics in experimental models (1, 33). According to the meta-analysis done by Wald, in moderate renal insufficiency was homocysteine about 5  $\mu\text{mol/l}$  higher than in normal subjects and this increase was associated with 42 % higher risk of cardiovascular death (10).

Mallamaci showed that homocysteine was significantly associated with atherothrombotic events in persons on chronic hemodialysis (11).

High plasma homocysteine level is a risk factor for mortality and vascular disease in observational studies in patients with CKD. It is known that folic acid and B vitamins decrease homocysteine levels in this population but it is unknown whether they decrease the mortality.

Jamison determined, whether high doses of folic acid, pyridoxin and cyanocobalamin administered daily, reduce mortality in patients with CKD. In a double-blind randomized controlled trial the author showed that levels of homocysteine were lower in the vitamin group of patients, but this treatment did not improve the survival or reduce the incidence of vascular disease in patient with CKD or ESRD (12).

### Asymmetric dimethyl arginine

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric-oxide synthase. ADMA is synthesized in many tissues. In the cardiovascular system it is produced in the heart, endothelium and smooth muscle cells. Exogenous ADMA inhibits nitric-oxide (NO) generation in vitro and in humans reduces blood flow and cardiac output and increases systemic vascular resistance and blood pressure. ADMA and its biologically inactive stereoisomer – symmetrical dimethylarginine (SDMA) – are not eliminated in patients with CRF. Thus, the concentrations of these substances in plasma are 2–6 times higher in uremic patients than in healthy control subjects (13). ADMA is now considered as one of the strongest marker of atherosclerosis (14). Elevated plasma concentrations of ADMA are associated not only with endothelial dysfunction and atherosclerosis but also predict mortality and cardiovascular complications in patients with CKD or ESRD (15). In subjects with mild to advanced CKD, plasma level of ADMA was inversely related to GFR and was an independent risk marker of mortality and progression to ESRD (16).

Two studies (Ravani, 2005, Fliser, 2005) showed that ADMA is a strong predictor of renal disease progression in patients with CKD. A high plasma concentration of ADMA is associated with

high cardiovascular risk in the general population, in persons with CKD and in ESRD patients (15).

In vitro, chronic inhibition of NO elaboration accelerates the progression of vascular lesions, whereas the supplementation with L-arginine (the precursor of NO) inhibits this progression. The absence of biologically active NO is associated with platelet aggregation and leukocyte adhesion. These mechanisms contribute to the development of acute athero-thrombotic events, which increase cardiovascular mortality rates (17).

Findings of interventional studies suggest that L-arginine supplementation improves endothelial dysfunction in patients with ESRD and in individuals with coronary artery disease (18).

### Troponin

Troponins are structural proteins of cardiac and skeletal muscles. There are three types of troponin (T, I, and C) that create the troponin complex. Cardiac troponin I and T are sensitive and specific markers of myocardial damage. However, in the absence of cardiac injury, troponins were found in clinical conditions such as ESRD, pulmonary embolism, acute stroke and sepsis (19).

Elevations of cardiac troponins in ESRD patients can result from many sources (Tab. 1). Patients with ESRD can have pathological changes in their skeletal muscles (uremic myopathy).

Some reports suggest that increased levels of troponin T could be the result of re-expression of fetal troponin T in myopathic skeletal muscles (20).

The second potential source can be silent myocardial injuries or microinfarcts, which are not detected by conventional investigations. Microinfarctions in these patients could be the result of silent ischemia, increased preload and nonischemic myocardial injury due to uremic toxins (19).

The next potential mechanism of elevated troponin T is the lack of clearance of cardiac troponins from the blood or alterations of their metabolism by nonfunctional kidneys (21). Left ventricular hypertrophy seems to be another cause of increased concentrations of troponin T in patients with ESRD. Mallamaci found the correlation between cardiac troponin and left ventricular hypertrophy in the dialysis patients, similarly Duman showed the same correlation in persons on continuous ambulatory peritoneal dialysis (22, 23). The results of many studies on prognostic significance of cardiac troponins are conflicting. In some studies, troponin T has a higher prognostic importance, in others, troponin I was found to be more powerful for the prediction of

**Tab. 1. Possible causes of cardiac troponin elevation in patients with ESRD (according to Bozbas, 2006).**

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Uremic myopathy
Expression of fetal cardiac troponins in skeletal muscles
Altered protein clearance
Abnormal protein metabolism
Silent myocardial injury, microinfarctions
Uremic toxins, Left ventricular hypertrophy

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cardiovascular events in the hemodialysis patients (24, 25, 26). However, according to results of all these studies, the prevalence of elevated levels of troponin T was more frequent than troponin I and therefore seems to have a higher prognostic value.

Cardiac diseases are a major cause of death in patients with ESRD, accounting for about 45 % of all deaths. In individuals receiving hemodialysis, about 20 % of cardiac deaths are attributed to an acute myocardial infarction (27). Performed studies suggested that in the absence of other signs and laboratory tests typical for an acute coronary ischemia, troponin T is a powerful predictor of mortality. So, increased levels of troponin in otherwise asymptomatic dialysis patients can reflect a silent cardiac ischemia or cardiomyopathy. Therefore, the US Food and Drug Administration approved the measurement of troponin T in dialysis patients for the risk stratification (28).

### B-type of natriuretic peptide

Natriuretic peptides are well-described family of hormones with a major role in sodium and body volume homeostasis. Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and D-type natriuretic peptide and their prohormones constitute the main members of this family. The synthesis and release of these peptides are stimulated by various derangements in systemic blood pressure as well as increases in intracellular volume and sodium balance. However, their major role is to induce natriuresis through their actions on renal hemodynamics and tubular function (29). Other effects of natriuretic peptides include vasodilation, inhibition of arginine vasopressin release, and inhibition of aldosterone release. In ESRD patients, their role in inducing natriuresis is limited (29).

Natriuretic peptides are responsible for the increase in extracellular volume sensed by atrial (ANP) and ventricular (BNP) stretch receptors (30).

Cardiovascular action of natriuretic peptides includes the reduction of blood pressure and preload, and the reduction of sympathetic tone in the peripheral vasculature (30). Natriuretic peptides also have an important antifibrotic, antiproliferative and anti-inflammatory properties and can act as local paracrine factors that antagonize the effects of the renin-angiotensin-aldosterone system. These actions could be important in subjects with ESRD in whom natriuretic peptides are elevated but natriuresis is severely reduced (29).

Levels of BNP and ANP are predictive of cardiovascular outcome in patients with ESRD (31). BNP is a strong predictor of adverse cardiovascular outcomes in persons with coronary heart disease and in subjects with systolic dysfunction. This remarkable high frequency of CKD (80–90 %) in these high risk populations suggest that these natriuretic peptides could be also useful for estimating the cardiovascular risk in patients with CKD (29).

It was shown that monitoring of plasma BNP concentration could be an advantageous method of screening for left ventricular dysfunction, especially in persons with a high cardiovascular risk and the measurement of BNP is useful to guide the treatment of heart failure (32).

### Conclusion

Among patients with CRF and ESRD, cardiac disease is the single greatest cause of mortality accounting for nearly one half of all deaths, and the mortality risk attributable to coronary heart disease is about 100 times higher than in general population. There is a strong and pervasive link between kidney failure and cardiac diseases. It is important to recognize those patients who are at the highest risk.

The alarming rate of cardiovascular events in the dialysis patients demands an accurate risk stratification to identify individuals at higher risk and therefore needing an intensive surveillance and treatment. It is known, that ESRD patients are treated much less intensively than they need to be treated. The limited prognostic value of traditional risk factors in ESRD implied that the attention should be focused also on other risk factors.

So, CRP could be an independent predictor of death in dialysis patients. Up till now, there is no evidence either in general population or in the dialysis population that lowering CRP levels leads to the decrease of cardiovascular risk. This biomarker conveys considerable prognostic information beyond traditional risk factors. BNP is a sensitive guide of the presence of left ventricular hypertrophy and left ventricular dysfunction in asymptomatic individuals and such characteristic have been confirmed in patients with ESRD. ADMA is a very important biomarker, which reflects the effects of various risk factors on endothelial function. Moreover, this substance is independently associated with mortality and cardiovascular events in dialysis patients. These biomarkers reflect a wide range of pathological processes involving atherosclerosis and the risk for thrombosis.

Cardiovascular risk stratification is important in the clinical management of patients with both CRF and ESRD, and biomarkers are increasingly used in these subjects.

Thus, CRP, BNP, ADMA and troponin can be involved in the diagnostic and therapeutic strategies for the detection and treatment of atherosclerotic complications and prevention of heart failure in this population.

### References

- Zoccali C.** Biomarkers in chronic kidney disease: utility and issues towards better understanding. *Curr Opin Nephrol Hypertens* 2005; 14: 1–6.
- Kurella M, Lo JC, Chertow GM.** Metabolic syndrome and the risk of chronic kidney disease among nondiabetic adults. *J Amer Soc Nephrol* 2005; 16: 2134–2140.
- Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Rogers NL, Teschan PE.** Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 1997; 51: 1908–1919.
- Mallamaci F, Tripepi S, Cutrupi S, Malatino LS, Zoccali C.** Prognostic value of combined use of biomarkers of inflammation, endothelial dysfunction, and myocardial pathology in patients with ESRD. *Kidney Int* 2005; 67: 2330–2337.
- Panichi V, Migliori M, De Pietro S et al.** C-reactive protein and interleukin-6 levels are related to renal function in predialytic chronic renal failure. *Nephron* 2002; 61: 594–600.

6. **Pecoits-Filho R, Heimbürger O, Barany P, Suliman M, Fehrman-Ekholm J, Lindholm B, Stenvinkel B.** Associations between circulating inflammatory markers and residual renal function in CRF patients. *Amer J Kidney Dis* 2003; 41: 1212–1218.
7. **Tonnelli M, Saks F, Pfeffer M, Jhangri GS, Curhan G.** Cholesterol and Recurrent Events (CARE) Trial Investigators. Biomarkers of inflammation and progression of chronic kidney disease. *Kidney Int* 2005; 68: 237–245.
8. **Tripepi G, Mallamaci F, Zoccali C.** Inflammation markers, adhesions molecules, and all-cause and cardiovascular mortality in patients with ESRD: searching for the best risk marker by multivariate modeling. *J Amer Soc Nephrol* 2005; 16 (Suppl 1): S83–S88.
9. **Roberts WL.** CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease. Application to Clinical and Public Health Practice. Laboratory tests available to assess inflammation — performance and standardization: a background paper. *Circulation* 2004; 110: 572–576.
10. **Wald DS, Law M, Morris JK.** Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *Brit Med J* 2002; 325: 1202.
11. **Mallamaci F, Zoccali C, Tripepi G, Fermo J et al.** CREED Investigators. Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. *Kidney Int* 2002; 61: 603–614.
12. **Jamison RL, Hartigan P, Kaufman JS et al.** Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. *J Amer Med Ass* 2007; 298: 1212–1214.
13. **Schiffrin EL, Lipman ML, Mann JFE.** Chronic kidney disease. Effect on Cardiovascular System. *Circulation* 2007; 116: 85–97.
14. **Cooke JP.** Asymmetrical dimethylarginine: the uber marker? *Circulation* 2004; 109: 1813–1818.
15. **Zoccali C, Bode-Boger S, Mallamaci F et al.** Plasma concentrations of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. *Lancet* 2001; 358: 2113–2117.
16. **Ravani P, Tripepi G, Malberti F, Testa S, Mallamaci F, Zoccali C.** Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: a competing risk modeling approach. *J Amer Soc Nephrol* 2005; 16: 2449–2455.
17. **Böger RH, Bode-Böger SM, Phivtong-ngam L et al.** Restoring vascular NO formation by L-arginine improves the symptoms of intermittent claudication in patients with peripheral arterial occlusive disease. *J Amer Coll Cardiol* 1998; 32: 1336–1344.
18. **Lerman A, Burnett JC Jr, Higano ST, McKinley LJ, Holmes DR Jr.** Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. *Circulation* 1998; 97: 2123–2128.
19. **Bozbas H, Yildirim A, Muderrisoglu H.** Cardiac Enzymes, Renal Failure and Renal Transplantation. *Clinical Medicine & Research* 2006; 1: 79–84.
20. **Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS.** Cardiac troponins in renal insufficiency: review and clinical implications. *J Amer Coll Cardiol* 2002; 40: 2065–2071.
21. **Ellis K, Dreisbach AW, Lertora JL.** Plasma elimination of cardiac troponin I in end-stage renal disease. *South Med J* 2001; 94: 993–996.
22. **Mallamaci F, Zoccali C, Parlongo S et al.** Cardiovascular Risk Extended Evaluation in Dialysis Investigators. Diagnostic value of troponin T for alterations in left ventricular mass and function in dialysis patients. *Kidney Int* 2002; 62: 1884–1890.
23. **Duman D, Tokay S, Toprak A, Duman D, Iktay A, Ozener IC, Unay O.** Elevated cardiac troponin T is associated with increased left ventricular mass index and predicts mortality in continuous ambulatory peritoneal dialysis patients. *Nephrol Dial Transplant* 2005; 20: 962–967.
24. **Iliou MC, Fumeron C, Benoit MO.** Prognostic value of cardiac markers in ESRD: Chronic Hemodialysis and New Cardiac Markers Evaluation (CHANCE) study. *Amer J Kidney Dis* 2003; 42: 513–523.
25. **Apple FS, Murakami MM, Pearce LA, Herzog CA.** Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation* 2002; 106: 2941–2945.
26. **Beciani M, Tedesco A, Violante A, Cipriani S, Azzarito M, Sturmiolo A, Splendiali G.** Cardiac troponin I (2nd generation assay) in chronic hemodialysis patients: prevalence and prognostic value. *Nephrol Dial Transplant* 2003; 18: 942–946.
27. **Apple FD, Murakami MM, Pearce LA, Herzog CA.** Multi-Biomarker Risk Stratification of N-terminal Pro-B-type Natriuretic Peptide, High Sensitivity C-Reactive Protein, and Cardiac Troponin T and I in End-Stage Renal Disease for All-cause Death. *Clin Chem* 2004; 50: 2279–2285.
28. **Cameron SJ, Geen GB.** Cardiac Biomarkers in Renal Disease: The Fog Is Slowly Lifting. *Clin Chem* 2004; 50: 2233–2235.
29. **Joffe S, Rossner MH.** Natriuretic peptides in ESRD. *Amer J Kidney Dis* 2005; 46: 1–10.
30. **Levin E, Gardner D, Samson K.** Natriuretic peptides. *New Engl J Med* 1998; 339: 321–328.
31. **Zoccali C, Mallamaci F, Benedetto FA et al.** Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Amer Soc Nephrol* 2001; 12: 1508–1515.
32. **Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM.** Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000; 355: f1126–1130.
33. **Krajcovicova-Kudlackova M et al.** Nutritional determinants of plasma homocysteine. *Bratisl Lek Listy* 2007; 108 (12): 510–515.

Received February 5, 2008.

Accepted June 15, 2008.