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Editorial

Multifactorial treatment for improvement of renal function and cardiovascular risk: an ATTEMPT for patients with metabolic syndrome and chronic kidney disease

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In this issue of *Current Medical Research and Opinion*, Athyros *et al.*[1] report the effects of long-term (up to 3½ years) multifactorial intervention on estimated glomerular filtration rate (eGFR) and serum uric acid (SUA) levels in 1123 patients with metabolic syndrome (MetS) but without diabetes mellitus (DM) or cardiovascular disease (CVD). The associations of the observed changes in renal function and SUA with CVD risk estimates and the number of CVD events were also assessed. These results were based on a post-hoc analysis of the ATTEMPT (Assessing The Treatment Effect in Metabolic syndrome without Perceptible diabeTes) study[2]. The authors evaluated these effects in all patients and in the subgroup with stage 3 chronic kidney disease (CKD) with an eGFR = 30–59 ml/min/1.73 m^2. Treatment aimed at a low density lipoprotein cholesterol (LDL-C) target of <100 mg/dl (n = 566) or <130 mg/dl (n = 557) achieved by appropriate doses of atorvastatin. Other components of the multifactorial intervention included lifestyle measures, antihypertensive, antiobesity and hypoglycemic treatment (for patients with impaired fasting glucose, IFG) and were similar between the study groups in terms of drugs and doses administered[1].

The main findings include significant increases in eGFR (by 3.5% in the whole study population, by 7.5% in those stage 3 CKD patients with LDL-C target of <130 mg/dl and by 11.1% in those stage 3 CKD patients with LDL-C target of <100 mg/dl) and reductions in SUA levels (by 5.6% in the whole study population, by 8.3% in those stage 3 CKD patients with the higher LDL-C target and by 10.7% in those stage 3 CKD patients with the lower LDL-C target)[1]. Similarly, the estimated 10-year CVD risk calculated using three risk engines was significantly reduced more in stage 3 CKD patients with LDL-C target of <100 mg/dl compared with those stage 3 CKD patients with LDL-C target of <130 mg/dl (Reynolds Risk Score: −71 vs. −55%; PROCAM Risk Score: −72 vs. −60% and Framingham Risk Score: −72 vs. −58%, respectively; $p < 0.001$ for all comparisons)[1].

Regarding CVD morbidity, during the 3½-year follow-up period, patients with stage 3 CKD and LDL-C target of <100 mg/dl did not have any CVD event, whereas the stage 3 CKD patients with LDL-C target of <130 mg/dl had six CVD non-fatal events ($p = 0.0014$)[1]. At the end of the study, the prevalence and the number of MetS components were significantly reduced in stage 3 CKD patients of both treatment groups (in a similar way); only 13% of patients in each group still had MetS[1].

The improvement in eGFR, SUA levels, CVD risk estimates and CVD morbidity in patients with stage 3 CKD were mainly attributed to the lipid-lowering and possibly the 'pleiotropic' properties of atorvastatin[1]. The administration of antihypertensive agents that block the renin–angiotensin–aldosterone system (RAAS), as well as treatment of obesity and IFG may have also provided cardio-renal protection[1]. In those stage 3 CKD patients with the lower LDL-C target greater changes in all parameters were observed, as well as absence of CVD events; the higher doses of atorvastatin administered in these patients were probably responsible for this difference as the remaining treatment was similar between the study groups[1].

As the authors point out[1], CKD has been consistently associated with increased risk for CVD morbidity and mortality[3–7]. A linear association has been reported between eGFR reduction and risk of CVD events[8]. Recent meta-analyses found that eGFR (negatively) and albuminuria (positively) were associated with all-cause and CVD mortality, independently of each other and of CVD risk factors, in both the general population[9] and patients with high-risk for CKD (i.e., individuals with DM, hypertension or CVD)[10]. Furthermore, renal dysfunction in patients with CVD or CVD equivalents [such as DM, peripheral artery disease (PAD) or carotid atherosclerosis] seems to increase the occurrence of CVD events or deaths[11–18].

Such findings led to the recognition of CKD, defined as eGFR <60 ml/min/1.73 m^2, as a CVD risk factor[19]. It has also been suggested that CKD may be a coronary heart disease equivalent[6]. Furthermore, as CVD is regarded as the main cause of mortality in individuals with renal impairment, treatment of CVD risk factors is relevant in these patients[20,21].

SUA has been also linked to vascular risk; several studies reported that hyperuricemia was associated with CVD morbidity and mortality[22–24]. These findings were also confirmed in meta-analyses[25,26]. Interestingly, similar results have been reported in patients with renal dysfunction[27–30], thus highlighting the role of SUA as a possible CVD risk factor in these patients. Furthermore, hyperuricemia has been suggested as a risk factor for CKD development[31,32] and progression[33,34]. Based on this evidence, there is a possible link between SUA, CKD and CVD[35].

In the Athyros *et al.*[1] study multifactorial intervention was shown to attenuate two potential CVD risk factors; CKD and SUA. Multifactorial treatment has several beneficial effects on both CVD and renal function, especially in high-risk patients such as those with MetS[36] and CKD[4,5]. Of note, statins were also shown to reduce SUA levels[37,38].

Antihypertensive treatment and especially drugs that block RAAS (i.e., converting enzyme inhibitors, angiotensin and aldosterone receptor antagonists) exert beneficial cardiovascular and renal effects[39]; improvements in proteinuria as well as prevention of CKD progression, CVD morbidity and mortality have been reported in relation to such antihypertensive therapy[40–42].

In obese patients with CKD weight loss should be recommended as it is associated not only with prevention of CVD and DM[43,44] but also with improvements in renal function[45]. Lifestyle measures such as diet and physical exercise are first-line options, followed by orlistat treatment and bariatric surgery in selected cases. The use of orlistat is generally safe, although rare cases of acute kidney injury have been reported[46]. New combination drug treatments for weight loss, such as naltrexone sustained-release (SR) + bupropion SR, are being assessed in clinical trials[47].

Hyperglycemia, even at levels lower than those required for the diagnosis of DM, has been associated with CVD[48]. In this context, antidiabetic drugs such as metformin[49,50] and pioglitazone[51–53] were shown to reduce CVD risk.

Smoking, both active and passive, is considered a major vascular risk factor[54–57]. A recent review[58] addressed the importance of smoking cessation in CKD patients.

Further research is needed to establish the value of multifactorial intervention in primary CVD prevention because the Athyros *et al.* study[1] has limitations. The results were based on a post hoc analysis of the ATTEMPT study. Furthermore, renal function was only assessed by eGFR. Other indices of kidney function such as cystatin-C, microalbuminuria and proteinuria have been also reported to influence CVD morbidity and mortality[59–64]. Of note, statin treatment was shown to improve these renal markers[20,64,65].

It was suggested that eGFR predicts CVD events and CKD outcomes better than microalbuminuria[66]. However, microalbuminuria is important for the early diagnosis of CKD (i.e., stages 1 and 2) enabling the prompt initiation of treatment for prevention of CKD progression and CVD incidence[67]. Even the presence of 'isolated' microalbuminuria (i.e., with normal eGFR) is associated with increased risk of CVD and CKD development[68]. Furthermore, the combination of eGFR and proteinuria was recently proposed as a better predictor of renal and CVD risk compared with either marker alone[69].

Finally, abnormal liver function tests (LFTs) and non-alcoholic fatty liver disease (NAFLD) has been linked to increased CVD morbidity and mortality[35]. Furthermore, statin-based therapy was shown to improve CVD outcomes in patients with abnormal LFTs[70,71] and NAFLD[72] with drug combinations (i.e. lipid-lowering, weight-reducing, antihypertensive and hypoglycemic) being more appropriate for NAFLD patients[73,74]. Interestingly, NAFLD has been associated with increased CKD incidence[75]. Additionally, lower eGFR correlated with increased transaminases and more severe NAFLD[76]. Of note, elevated SUA levels have been related to the presence of

NAFLD, independently of several confounding factors such as age, gender, body mass index, smoking, blood pressure, glucose, lipids and gamma-glutamyltransferase[35]. Therefore, future studies should evaluate LFTs and NAFLD in patients with CKD and assess the effectiveness of multifactorial treatment with regard to SUA levels, renal and liver function as well as CVD prevention.

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