

## Editorial:

# Preventing Cardio-renal Syndrome Rather than Treating It: Could Statins Play A Role?

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Cardiorenal syndrome (CRS) is the umbrella term used to describe clinical conditions in which renal dysfunction accompanies cardiac failure or cardiac dysfunction accompanies renal failure [1, 2]. There are 5 types of CRS (Table 1). The rising prevalence of chronic kidney disease (CKD) and heart failure (HF), contributed to the increase of the incidence of CRS, which was further increased by the improved survival of patient with HF, CKD or both [3, 4]. The heterogeneous and complex pathophysiology of CRS makes effective patient management difficult. Established therapeutic strategies, such as diuretics, are often associated with resistance and limited clinical success [3, 5].

Fabian *et al.* [6] provide useful data about CRS. The percentage of patients with the syndrome is relatively high among patients admitted in an Internal Medicine Ward (1 in 7 patients). In CRS, HF and CKD shared a substantial number of risk factors [6], such as old age, arterial hypertension, diabetes mellitus (DM), and history of cardiovascular disease (CVD) [6].

Despite the fact that Fabian *et al.* do not report mortality rates they support that "women with glomerular filtration rate (GFR) 30-44 ml/min/1.73m<sup>2</sup> and men with GFR 30-50 ml/min/1.73m<sup>2</sup> but without history of CVD had a hazard ratio for CVD of 1.51 that increased to 2.39 in those with CVD history. Worsening of renal function is also an independent predictor of mortality in acute decompensated heart failure (ADHF)." Moreover, it has been established that individuals with CKD are more likely to die of CVD than to develop kidney failure [7]. Thus, given the poor prognosis of CRS [3,5] Fabian *et al.* suggest that prevention is a priority [8].






Some of the measures of CRS prevention are focused, according to CRS type, on preventing decompensation of stable HF, optimal medical and device treatment of HF with blood pressure and volume control, prevention of acute renal injury (AKI), attenuating the progression of CKD, and treatment of the underlying systemic disease to reduce end-organ injury [3,5].

CRS is a haemodynamic derangement ranging from acute pulmonary oedema, with hypertension through severe peripheral fluid overload, to cardiogenic shock and hypotension [9]. However, its pathophysiology is much more complex than simply reduced cardiac output or renal dysfunction. Factors such as nitric oxide, prostaglandin, natriuretic peptides, and endothelin may mediate renal perfusion independently of cardiac haemodynamics and vice versa [10].

There are some "established" measures for the prevention or the treatment of CRS. One of these is renin-angiotensin-aldosterone system (RAAS) blockade [5]. Many trials confirmed the benefits of angiotensin enzyme inhibitors (ACEI), such as Studies of Left Ventricular Dysfunction (SOLVD), in the treatment of HF [11]. However, SOLVD excluded patients with serum creatinine concentrations > 2.0 mg/dL. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) [12] in patients with severe HF, included patients with renal impairment, but only if their serum creatinine concentrations were < 3.4 mg/dl. Although only a minority of patients in CONSENSUS had creatinine levels > 2.0 mg/dL, this subgroup showed evidence of improved outcomes when treated with an ACEI [12]. Some of those experienced a serum creatinine increased by 30% or greater with enalapril [12]. However, creatinine tended to stabilize and in many patients improved throughout the study. Therefore, it has been suggested that RAAS blockade may be carefully titrated provided that serum creatinine does not continue to rise beyond 30% and potassium is constantly < 5.0 mmol/L [13]. ACEI therapy in patients with baseline renal insufficiency is associated with significant long-term

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Table 1. Types of Cardiorenal Syndrome

Type of Cardiorenal Syndrome	Definition	Primary Event
Acute cardio-renal (type 1) (20–25%) 	Acute worsening of heart function (AHF–ACS) leading to kidney injury and/or dysfunction	Acute heart failure (AHF) or acute coronary syndrome (ACS) or cardiogenic shock
Chronic cardio-renal (type 2) (30–45%) 	Chronic abnormalities in heart function (CHF–CHD) leading to kidney injury or dysfunction	Chronic heart disease (systolic and/or diastolic dysfunction, chronic abnormalities in cardiac function, cardiomyopathy)
Acute reno-cardiac (type 3) (30–35%) 	Acute worsening of kidney function leading to heart injury and/or dysfunction	Acute kidney injury (AKI)
Chronic reno-cardiac (type 4) (45–50%) 	Chronic kidney disease (CKD) leading to heart injury, disease and/or dysfunction	CKD
Secondary cardio-renal (type 5) 	Systemic condition causing cardiac and renal dysfunction	Systemic disease (septic shock, diabetes, MetS, NAFLD, amyloidosis, vasculitis etc.)

AHF = Acute heart failure, ACS = acute coronary syndrome, AKI = acute kidney injury, CKD = chronic kidney disease, MetS = Metabolic syndrome, NAFLD = non alcoholic fatty liver disease.

benefits [14], and unless contraindicated, should be routinely used [5]. Most patients who are already on an ACEI and develop renal insufficiency during hospitalization for HF decompensation should not have their ACEI stopped. In general, ACEI use is not associated with worsening renal function in these patients [15]. However, clinical judgment should be used in patients with cardiogenic shock or acute renal failure [14].

Blockade of the sympathetic system with beta-blockers is another important strategy for patients with congestive HF or CHD [13]. In general, these drugs should not adversely affect kidney function. Certain beta-blockers may be relatively contraindicated in CKD because of metabolism by the kidney, such as atenolol, nadolol or sotalol [16]. Carvedilol has been demonstrated to have favourable effects on kidney function in some CRS patients, and may have a benefit over older beta-blockers [17].

Both congestive HF and CKD are associated with anaemia, the latter of which is commonly treated with erythropoiesis-stimulating agents [18], and there is interest in using erythropoiesis-stimulating agents in HF patients [19]. However, other studies did not find significant improvement in a variety of important clinical parameters [20]. Moreover, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [21] reported that patients with a poor response to darbepoetin alfa, compared with those with a better response, had higher rates of the composite CVD end point

[adjusted hazard ratio (HR), 1.31; 95% confidence interval [CI], 1.09 to 1.59) or death (adjusted HR, 1.41; 95% CI, 1.12 to 1.78), as doses were increased to attain target haemoglobin levels. These findings raise concern about current strategies for treating anaemia in patients with CKD [21].

However, it seems that there is a treatment that potentially improves both cardiac and renal function and practically remains unused in the effort to prevent CRS: effective statin treatment with a specific compound at specific doses [22].

It was shown in a *post hoc* analysis of the Treating to New Targets (TNT) study (n = 10,001) that 80 mg/day of atorvastatin compared with the 10 mg/day dose, in patients with stable coronary heart disease (CHD) significantly reduces hospitalizations for HF [23]. However, this benefit was mainly shaped by CHD patients with a history of HF (7.8% of study population) [23]. In this subgroup the incidence of hospitalizations was substantially less in the 80 mg/day group than those with a 10 mg/day group [17.3 vs 10.6% in the 10- and 80-mg arms, respectively (HR 0.59; 95% CI 0.4 to 0.88; P=0.009)] [23]. Similar were the results of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study [24] that we reported 5 years earlier than TNT. A *post hoc* analysis of the Scandinavian Simvastatin Survival Study (4S) in 1997 [25] showed that mortality was 31.9% in the placebo group and 25.5% in the simvastatin group among patients who developed HF. These

were substantially higher than the mortality rates of non-HF patients (9.2 and 6.6%, respectively), however, the reduction in mortality and hospitalizations were comparable among HF and non-HF patients [25]. Still, this is the heart end of the CRS. The issue is to cover both the heart and kidney.

Early CKD (up to stage 3; the stages of CKD are reported in Table 2) could be slowed down [26] or even reversed by statins which on the other hand substantially reduce CVD events [22, 27-30]. Uncontrolled dyslipidaemia induces a renal function impairment that ranges from 1 to 12 ml/min/1.73m<sup>2</sup> per year, particularly in the presence of diabetes (DM) or arterial hypertension [27,29]. A large study with 40 mg/day of simvastatin (the Heart Protection Study, n=20,000) [31] and a joint analysis of pravastatin trials [32] showed that these statins reduce the rate of the (expected with age and CVD risk factors) kidney function decline in patients with or at risk of CVD. In the GREACE study, we showed for the first time that atorvastatin treatment significantly increases eGFR. In contrast, eGFR was reduced in untreated patients with CHD with or without metabolic syndrome (MetS) or DM [33-35]. This improvement of renal function was clinically relevant and associated with substantially reduced CVD events [33]. With every 5% in eGFR increase there was a reduction of 16% in clinical vascular events, after multiple regression analysis adjusting for major covariates [33]. Thus, with a 10% increase of eGFR in stage 2 and 3 CKD patients in GREACE we recorded a 32% further (independent of LDL-C) reduction in clinical events [33]. A substantial benefit of atorvastatin treatment was also seen in the large TNT trial (n = 10,001 patients with stable CHD) [36,37]. In stage 3 CKD TNT patients, the increase in eGFR was significantly greater with atorvastatin 80 mg/day than with 10 mg/day (9.9 vs 6.6%, respectively; p < 0.005) [36]. In patients with stage 3 CKD (n = 3,107) the HR for CVD events was 31.9% higher than those without CKD (n = 6,549), regardless of atorvastatin dose [36]. Nevertheless, compared with atorvastatin 10 mg/day, the 80 mg/day dose reduced the relative risk of major CVD events significantly more in those with CKD (by 32 vs 15% in those with normal renal function) [37]. This reduction shaped the overall TNT outcome and was identical with the one we recorded in GREACE [33]. In the Collaborative Atorvastatin Diabetes Study (CARDS) [38], a randomized placebo-controlled trial that included 2,838 patients with type 2 DM and free of CVD at baseline, 34% of the patients had stage 3 CKD (eGFR of 30-59 ml/min/1.73m<sup>2</sup>-Table 2). In these patients

atorvastatin 10 mg/day was associated with a moderate improvement in the annual change in eGFR (p = 0.01). This was accompanied by a substantial reduction in major CVD events (total mortality plus non-fatal myocardial infarction: -42%) and stroke (-61%) [38], compared with placebo.

In GREACE, TNT and CARDS, the control of other CVD risk factors (except dyslipidaemia) was similar in the atorvastatin and placebo (or usual care for GREACE) groups; therefore the improvement in renal function and the clinical benefit in terms of CVD event reduction is attributed to atorvastatin use. This stage 3 CKD patient group is a substantial part of secondary prevention patients (32 to 34% in all 3 of the studies above) and benefited most from lipid-lowering in all 3 studies. In the above studies in patients effectively treated with statins there were less acute coronary events (less ground for type 1 CRS), less cases with congestive HF (less ground for type 2 CRS) and fewer cases with CKD, because statin treatment halted the evolution of kidney impairment or even reversed it. Thus, there was less ground for type 4 CRS and if CKD is the perfect substrate for acute kidney impairment after haemodynamic derangement, less ground for type 3 CRS. Even type 5 CRS could be prevented, at least in part, with statin treatment. There is a positive impact of managing atherogenic dyslipidaemia on CVD outcome across all stages of diabetic nephropathy [29], MetS [39], non alcoholic fatty liver disease (NAFLD) [40], or systemic autoimmune diseases (SAD) [41]. CVD is the leading cause of morbidity and mortality in patients with SADs [42]. Patients with systemic lupus erythematosus (SLE) are 5-6 times more likely to have a significant coronary event than the general population [43]. Rheumatoid arthritis (RA) is also associated with an increased CVD risk resulting in early mortality and excess morbidity [42-44]. However these diseases also affect renal function [45]. Both CVD and CKD might be effectively managed, to some extent, by statins [42]. Both CVD and CKD in the above diseases are related to low grade inflammation, endothelial dysfunction-low NO levels, oxidative stress, instability of atherosclerotic plaques and a pro-coagulant state related to atherosclerosis [41,46]. There is evidence that these factors could be controlled by the pleiotropic (cholesterol-lowering-independent) effects of statins [46]. These effects are enhanced by even a small increase in high density lipoprotein cholesterol levels [47], and are evident even in patients with mild renal impairment [48].

All the above suggest that the use of ACEI and statins might be an effective regimen to prevent a substantial num-

**Table 2. Stages of Chronic Kidney Disease**

	Description	GFR ml/min/1.73m <sup>2</sup>
Stage 1	Kidney damage with normal or increased GFR	≥ 90
Stage 2	Kidney damage with mildly decreased GFR	60-89
Stage 3	Moderately decreased GFR	30-59
Stage 4	Severely decreased GFR	15-29
Stage 5	Kidney failure	< 15 or dialysis

GFR = glomerular filtration rate.

ber of CRS cases in high risk patients and improve survival and quality of life in these people. There are data suggesting that combined use of a statin plus an ACEI improves clinical outcome more than a statin alone and considerably more than an ACEI alone [30]. After all, recent guidelines suggest that CKD is a high CVD risk situation [49,50]. This requires aggressive statin treatment.

## DISCLOSURE

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## CONFLICT OF INTEREST

There is no conflict of interest.

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