Cardiovascular Death in Uremia—More Complex Than We Thought

Eberhard Ritz

A brief overview is provided of the history of cardiovascular complications in renal disease and the underlying pathomechanisms involved in the acceleration of atherogenesis in the earliest stages of renal malfunction. Coronary artery disease versus cardiomyopathy as the cause of cardiac death in renal patients is discussed. Interventions to attenuate the progression of chronic kidney disease, such as blood pressure lowering, treatment with statins and beta-blockers, and blockade of the renin-angiotensin system, are also covered. [Hong Kong J Nephrol 2008;10(1):7–13]

Key words: cardiovascular risk, chronic kidney disease, hemodialysis

HISTORY OF CARDIOVASCULAR COMPLICATIONS IN RENAL DISEASE

When maintenance hemodialysis became available, it was—somewhat naively—widely thought that washing out uremic toxins would prolong the life expectancy of uremic patients to the level found in the general population. A report from Seattle where maintenance hemodialysis had started came as a rude surprise when it indicated that almost 50% of the patients initially on maintenance hemodialysis had died within slightly more than 10 years time, mostly from cardiac causes. The authors postulated that atherosclerosis is accelerated in patients on prolonged hemodialysis [1]. The high cardiovascular mortality of patients on dialysis has been widely confirmed and found to be higher than in the background population by a factor between 5 and 500 depending on age [2]. Nevertheless, it had remained controversial for a long time whether excess cardiovascular mortality was actually due to specific acceleration of atherogenesis, because an alternative possibility had not convincingly been excluded, i.e. that the high cardiac death rate resulted from the high prevalence of classical cardiovascular risk factors.

Meanwhile, it has been firmly established that cardiovascular risk starts very early in chronic kidney disease (CKD). Unexpectedly, it was found that even in advanced CKD, the risk to go on renal replacement therapy is substantially lower than the risk to die, mostly from cardiovascular causes [3] (Table 1).

The recognition that even minor renal dysfunction predicts elevated mortality goes back to the Hypertension Detection and Follow-up Program (HDFP), which documented a significant increase in 10-year mortality even for patients with serum creatinine concentrations between < 1.2 mg/dL and 2 mg/dL [4]. A more recent study from Belgium calculated estimated glomerular filtration rate (eGFR) in apparently healthy individuals and noted that the risk of death was increased even within the bracket of eGFR values 89.4–104.3 mL/min/1.73 m² [5] (Table 2).
The risk conferred by impaired renal function is particularly high in patients suffering from coronary events or cardiac malfunction. In patients with creatinine clearance > 75 mL/min undergoing myocardial infarction, inhospital mortality was 2% [6]. In contrast, in patients with creatinine clearance 50–75 mL/min, it was increased by a factor of 3 (6% mortality), and in end-stage renal disease by a factor of 15 (30% mortality). Similarly, the post-discharge death rate was strikingly increased in CKD. It has recently been noted that GFR alone is not the only determinant. At any given level of GFR, the cardiac risk is increased if the patient has proteinuria [7], and this is true even for microalbuminuria [8].

**UNDERLYING PATHOMECHANISMS**

Recent experimental work [9,10] shows that in a genetic model of accelerated atherogenesis, the apo E−/− mouse, the rate of growth of aortic plaques is accelerated after subtotal nephrectomy, but amazingly this is found even after uninephrectomy. The study of Bursztyn et al [11] documented in hypertensive patients that the coronary calcium score increased more rapidly over a 3-year observation period if eGFR was < 60 mL/min.

These observations raise the question about the underlying pathomechanisms involved in such acceleration of atherogenesis in the earliest stages of renal malfunction.

Presumably, the most important factor is endothelial dysfunction which is demonstrable even in early stages of CKD. In the MMKD study, we noted in patients with primary kidney disease that even when the measured GFR was normal, the concentration of ADMA (asymmetric dimethyl-L-arginine) was increased [12]. This is presumably explained by the fact that despite progressive loss of nephrons, whole kidney GFR is initially kept normal by compensatory single nephron hyperfiltration. The metabolically relevant number of tubular epithelial cells is already diminished, however. With respect to ADMA, this is important because breakdown of ADMA via DDAH (dimethylarginine dimethylamino hydrolase) takes place in tubular epithelial cells. Some further abnormalities at this stage of CKD with normal whole kidney GFR include: abnormal Apo lipoproteins [13, 14] and increased sympathetic activity [15]. In addition, in patients with IgA-glomerulonephritis who were normotensive according to the WHO criteria and had normal GFR, we found already increased blood pressure, particularly at night time. Further abnormalities relevant to atherogenesis are found in CKD and include: a proinflammatory state, indicated by elevated high sensitivity C-reactive protein, fibrinogen, interleukin-6 and intercellular adhesion molecule; as well as a prothrombotic state, indicated by increased D-dimers [16].

The ultimate culprit appears to be the endothelial cell. An endothelial cell abnormality is suggested by the observation of Landray et al [17]: in patients with primary kidney disease, increasing quintiles of cystatin C (a marker of GFR) are associated with progressively elevated concentrations of von Willebrand factor. Von Willebrand factor is an index of endothelial cell dysfunction.
Based on our partially unpublished experimental studies [9], we propose the hypothesis summarized in Table 3: minor derangements of renal function cause dysfunction of endothelial cells with increased oxidative stress as the presumed common denominator.

Apart from injury by a primary kidney disease, another aspect deserves mention. Both experimental studies [18] and human observations [8,19] document that impaired intrauterine development is associated with a diminished number of nephrons, thus introducing a higher risk of microalbuminuria [19] and diminished GFR [8]. This may be a complementary explanation for the link between faulty prenatal programming and increased risk in adult life with higher cardiovascular as well as renal risk and event rates (Figure). Diminished nephron number [20] in and by itself is presumably not sufficient to lead to progressive renal dysfunction, but may explain why individuals born with low birth weight have higher albumin-creatinine ratios at young adult age [21] and presumably experience more rapid loss of renal function when in adult life and additional renal insult occurs, e.g. diabetes, IgA glomerulonephritis etc.

### Table 3. Endothelial cell dysfunction in chronic kidney disease

<table>
<thead>
<tr>
<th>Minor derangements of renal function (microalbuminuria, loss of glomerular filtration)</th>
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<tr>
<td>• Dysfunction of endothelial cells</td>
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**CORONARY ARTERY DISEASE VERSUS CARDIOMYOPATHY**

In the past, it was thought that the great majority of renal patients die from coronary heart disease. Recent studies, for instance the German 4-D study [22], found that adjudicated coronary heart disease accounted for only 9% of deaths whilst other cardiac causes accounted for 35% (i.e. sudden death for 26%, heart failure for 6%, other cardiac causes for 3%). This finding prompted us to argue that, apart from coronary disease, cardiomyopathy is a major cause of cardiac death in renal patients. Potential explanations for cardiomyopathy (Table 4) include inappropriate cardiac hypertrophy (both of the left and right ventricle which excludes hemodynamic causes as a simple explanation), interstitial fibrosis and microvessel disease with wall thickening of postcoronary arteries and microvessel disease (capillary deficit and arteriolar thickening).

These alterations contribute to systolic dysfunction, diastolic dysfunction and electrical instability in patients with renal disease. Such cardiomyopathy starts early on in the course of CKD. In unpublished studies,
we found that expansion of the cardiac interstitium, reduction of the capillary density in the myocardium and thickening of intramyocardial arteries occurred even after uninephrectomy. The important role of reactive oxygen species is suggested by the observation that such abnormalities were completely prevented by the administration of tempol, a superoxide-dismutase agonist, which prevents formation of reactive oxygen species.

**INTERVENTIONS**

The observation of excess cardiovascular mortality in the early stages of CKD [3] is of course bad news, but the good news is that all interventions that are necessary to attenuate progression of CKD are also beneficial for the heart (“what is good for the kidney is also good for the heart”):

- lowering of blood pressure;
- blocking the renin-angiotensin-aldosterone system;
- lowering lipids;
- cessation of smoking;
- fighting the metabolic syndrome and others.

This has led to recent discussions on whether kidney disease should be considered as a coronary heart equivalent, similar to diabetes mellitus for which guidelines recommend interventions as if the patient had survived myocardial infarction [23]. Timely intervention in the early stages of CKD is also important for another reason: in a somewhat underpowered study, it was shown that in advanced CKD (stage IV or V), multiple risk factor intervention as compared to conventional care, i.e. intensified treatment, conferred no longer significant benefit with respect to cardiovascular events, carotid intima thickness and brachial artery reactivity as an index of endothelial function [24].

Unfortunately, only limited controlled prospective evidence is available for the selection of treatments in patients with advanced CKD. The importance of this concern is illustrated by the observation that although some parameters such as homocysteine [25] had been highly predictive of cardiovascular events, yet their (partial) correction failed to yield a significant benefit as illustrated by the failure to lower homocysteine by administering folate [26].

There have been a number of recent reports, indicating that in observational studies, patients treated with active vitamin D had lower all cause and cardiovascular mortality [27]. This fascinating observation must, however, again be confirmed by prospective interventional data. Admittedly, however, the fact that active vitamin D suppresses renin expression in the juxtaglomerular apparatus [28] provide a very strong rationale as do other observations.

Interventions of (more or less) proven benefit include lowering of blood pressure, lipid lowering, beta-blocker treatment and blockade of the renin-angiotensin system.

**Blood pressure lowering**

With respect to the optimal blood pressure on dialysis, there has been considerable controversy. On the one hand, the center in Tassin [29], using long slow dialyses, noted that the 15-year survival was better by 24% in patients whose mean arterial pressure was < 99 mmHg (Table 5). Observational studies in patients on relatively short-term dialysis showed: no relation of blood pressure to survival (as did the German 4-D Study [22]); a relation only to high pulse pressure [32] as an index of aortic stiffening.

### Table 5. Better survival of hemodialysis patients with low normal as compared to upper normal blood pressure values: Tassin dialysis center—patient survival as a function of mean arterial pressure (MAP)

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>5 yr</th>
<th>10 yr</th>
<th>15 yr</th>
<th>20 yr</th>
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<td>&lt; 99</td>
<td>93</td>
<td>85</td>
<td>67</td>
<td>53</td>
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<td>≥ 99</td>
<td>81</td>
<td>65</td>
<td>43</td>
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[From Reference 29.]
The explanation for the contraintuitive survival benefit of high and mortality excess at low blood pressures in some studies is the presence of reverse causality, i.e. the association between risk factors and outcome is confounded by preexisting comorbidities. In other words, if patients are no longer able to generate a sufficiently high blood pressure because of cardiac disease, they die—not (at least not exclusively) because blood pressure is low, but because of concomitant heart malfunction that no longer allows them to generate a normal or high blood pressure.

In our view, low blood pressure in patients relatively recently accepted for maintenance hemodialysis is a predictor of early mortality, while low blood pressure in patients on long-term hemodialysis with more optimized dialysis schedules (particularly long slow dialysis) is a predictor of better survival. It follows that the issue of whether or not high blood pressure on dialysis should be treated should be individualized.

**Statin treatment**

Despite the negative outcome of the German 4-D study [22], we still believe that statins are a useful agent in the treatment of CKD patients, at least those with CKD or dialysis patients with manifest coronary heart disease. Controlled prospective trials on patients with diabetes or heart disease, particularly those with mild to moderate impairment of renal function, showed that they obtained major benefit from statins [33]. The argument is rendered even more interesting by the recent result of a meta-analysis indicating that treatment of CKD patients with statins is associated with minor, but statistically significant, less loss of renal function [34]. The negative outcome in the 4-D study is mainly explained by the relatively low frequency of adjudicated coronary death (which is apparently responsive to statin treatment) because lowering of low-density lipoprotein cholesterol by 1 mmol achieved a 19% reduction in coronary deaths—exactly what had been observed in non-dialysed patients. Apparently, the other causes of death are not due to cardiac ischemia resulting from coronary disease and the final answer will have to wait for the sufficiently powered SHARP study.

An alternative, or complementary explanation, may be that in uremic compared to non-renal patients with coronary heart disease, the coronary plaques show more intense inflammatory changes (higher C-reactive protein, terminal complement complex C5b-9) and more intense macrophage infiltration, expression of markers of fibrosis (transforming growth factor-β, collagen IV, endothelin 1) and, particularly, more intense deposition of glycophorin, an erythrocyte membrane protein, evidence of past hemorrhage into coronary plaques [35].

It has recently been claimed that statins reduce the risk of septicemia in CKD patients, a finding that we could not confirm in the 4-D study.

**Beta-blockers**

In an observational study on hemodialysed type 2 diabetic patients, Koch et al [36] noted that only 4% of patients who died, but 12% of patients who survived, had received beta-blockers; the same had been observed in the URREA study [37].

In dialysed patients with dilated cardiomyopathy, Cice et al [38] observed that the rate of cardiovascular death in patients randomized to receive placebo was 67.9%, whereas that of patients randomized to receive carvedilol was 29.3%, and a similar reduction was seen with respect to hospitalization.

There is very little chance that a prospective randomized trial of beta-blockers with adequate size will ever be performed in dialysis patients. The available evidence, however, would strongly suggest that beta-blockers be used, particularly in view of the excess sympathetic activity in patients on dialysis [39] and the frequency of sudden death [40]. Because of the many metabolic and circulatory side effects of classical beta-blockers, we prefer the use of carvedilol [41] or nebivolol.

**Blockade of the renin-angiotensin system**

In the PEACE trial on the use of trandolapril in patients at low cardiovascular risk, the overall result was completely negative. Surprisingly, however, Solomon et al [42] noted that in patients with eGFR < 60 mL/min, trandolapril treatment achieved significant benefit, suggesting either that the renin-angiotensin system is more activated in early CKD or that it is more responsive to blockade. The administration of angiotensin-converting enzyme inhibitors (ACEIs) in patients with early and advanced CKD is safe, particularly with respect to hyperkalemia [43], but unfortunately, in elderly hemodialysed patients, per protocol analysis of a French study found no significant benefit from fosinopril (relative risk, 0.79; p < 0.09) [44]. Thus, there is currently no controlled evidence for the efficacy of ACEIs.

The situation is somewhat better with respect to angiotensin receptor blockers (ARBs). In an unpublished study, Cice found that hemodialysis patients with heart failure who had received telmisartan on top of alternative therapy, including ACEIs, had significantly (p < 0.01) better survival over 36 months. This result (presented so far only in abstract form) requires confirmation.

Some small preliminary underpowered Japanese studies suggest less cardiovascular mortality in patients on ARBs and a larger study is currently ongoing.

One important consideration is the fact that blockade of the renin-angiotensin system increases the duration of residual diuresis, which is a most powerful predictor of survival [45]. It has been shown that while diuretics augment residual diuresis, they fail to prolong its
In contrast, prospective studies in peritoneal dialysis patients documented that both ramipril [47] and valsartan [48] prolonged persistence of residual diuresis.

Finally, a study on 43,200 prevalent hemodialysis patients of the Gambro Healthcare System in the USA with 729 cases of cardiac arrest found that the relative chance of survival was improved by beta-blockers (odds ratio, 0.60) and by ACEIs or ARBs (odds ratio, 0.53) [49].

**REFERENCES**


