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Epidemiology and Prevention of Cardiovascular Complication in Chronic Kidney Disease Patients

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The risk for cardiovascular disease is significantly higher among patients with chronic kidney disease (CKD) than among the general population, considering that cardiovascular disease is the prominent cause of both morbidity and mortality in dialysis patients. This is explained mainly by the considerable prevalence of cardiovascular risk factors among CKD patients since the earliest stages of renal impairment, which include not only the so-called traditional risk factors, but also a number of additional risk factors that are specific to CKD and to the dialytic treatment itself. Considering the multiplicity of cardiovascular risk factors operating in CKD patients, as well as the crucial impact of their cardiovascular condition on long-term outcome, it is mandatory that all the available interventions aimed at the correction of all the modifiable risk factors for cardiovascular disease are performed as early as possible in the progression of the disease. In particular, the results of several controlled clinical trials have shown that a timely correction of anemia and of calcium-phosphate disorders leads to a significant improvement in the cardiovascular conditions of CKD patients. Evidence also is growing regarding the benefits of intervention of newly recognized risk factors for cardiovascular disease such as inflammation and oxidant stress.

KEYWORDS chronic kidney disease, cardiovascular disease, end-stage renal disease, anemia, hyperphosphatemia, dyslipidemia, inflammation, oxidative stress

The risk for cardiovascular disease is significantly higher among patients with chronic kidney disease (CKD), particularly during end-stage renal disease (ESRD), than among the general population. Cardiovascular disease is indeed the prominent cause of morbidity and mortality in dialysis patients, being responsible for almost 50% of deaths[1,2] and nearly 40% of hospitalizations.[1] The adjusted cardiovascular mortality rate in ESRD patients is approximately 10 to 20 times higher than that in the general population when considering the whole dialysis population, and approximately 1,000 times higher when limiting the analysis to younger patients.[3]

The main reason for such a high prevalence of cardiovascular complications in the CKD population is the considerable prevalence of cardiovascular risk factors since the earliest stages of renal impairment, which also explains the considerably high proportion of patients with impaired cardiovascular conditions when starting renal replacement treatments.[1,4,5] In more than 400 incident hemodialysis patients enrolled in the Effect of Membrane Permeability on ESRD Patient Outcome (MPO) study, a multicenter trial that still is ongoing in 59 hemodialysis centers across Europe, the prevalence of coronary heart disease, cerebrovascular disease, and peripheral vascular disease was found to be 13.1%, 7.2%, and 14.0%, respectively, in the entire study population, although these percentages were significantly different between patients enrolled in the North versus the South of Europe.[6] These results, although similar to those observed in another multicenter, prospective trial performed on incident hemodialysis patients, the Netherlands Cooperative Study on the Adequacy of Dialysis,[7] are significantly lower than those observed in a sample of more than 1,000 European patients randomly selected from the Dialysis Outcomes and Practice Patterns Study population.[8] This is probably owing to the fact that, unlike the Effect of Membrane Permeability on ESRD Patient Outcome study in which a strict compliance with current practice guidelines was requested by the protocol for the patients to be enrolled, the Dialysis Outcomes and Practice Patterns Study is a more accurate reflection of the hemodialysis population seen in everyday clinical practice.

A significant percentage of patients already are affected by

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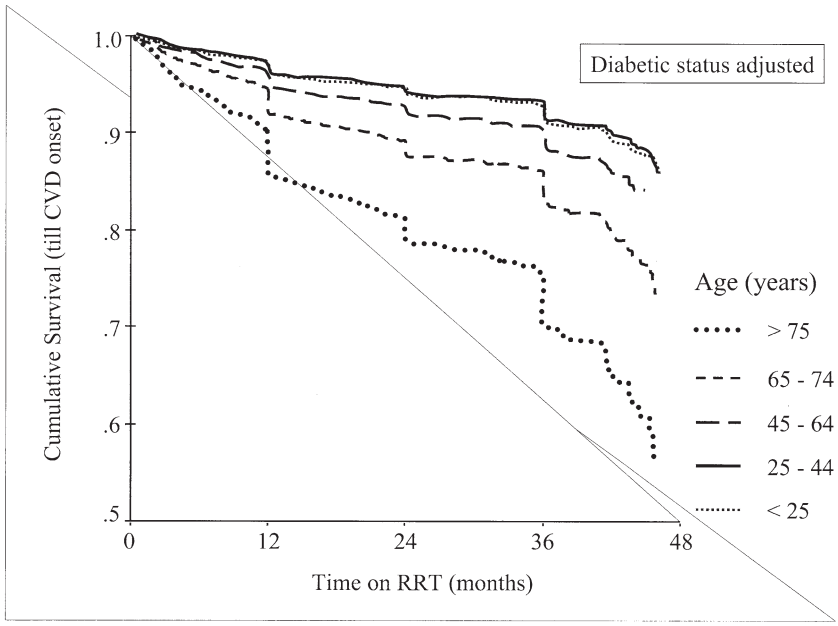

Figure 1 Risk for the development of de novo cardiovascular disease according to age at the start of dialysis. Relative risk = 1.03, 95% confidence interval = 1.02-1.04, $P < .0001$.

cardiovascular disease when they start dialysis or probably will develop it very soon, independently of the chosen dialytic modality,[9] with older age and diabetes mellitus being the 2 most important risk factors for the development of de novo cardiovascular disease (Figs. 1 and 2). Cardiovascular abnormalities are already highly prevalent in patients with all the degrees of CKD. As shown by an echocardiographic evaluation of predialysis patients with varying degrees of CKD, the prevalence of left ventricular hypertrophy (LVH), which is echocardiographically evident in approximately 70% of patients starting dialysis,[4] was found to be nearly 30%, even in those patients with so-called mild renal insufficiency (creatinine clearance of 50–75 mL/min) and tended to increase progressively with the decrease in renal function.[10] In a recent analysis of baseline characteristics of 581 patients with a creatinine clearance of 15 to 35 mL/min enrolled in the Cardiovascular Reduction Early Anemia Treatment with Epoetin β study, 26% of the patients had congestive heart failure, 17% had ischemic heart disease (coronary artery disease and/or myocardial infarction), 6% had cerebrovascular dis-

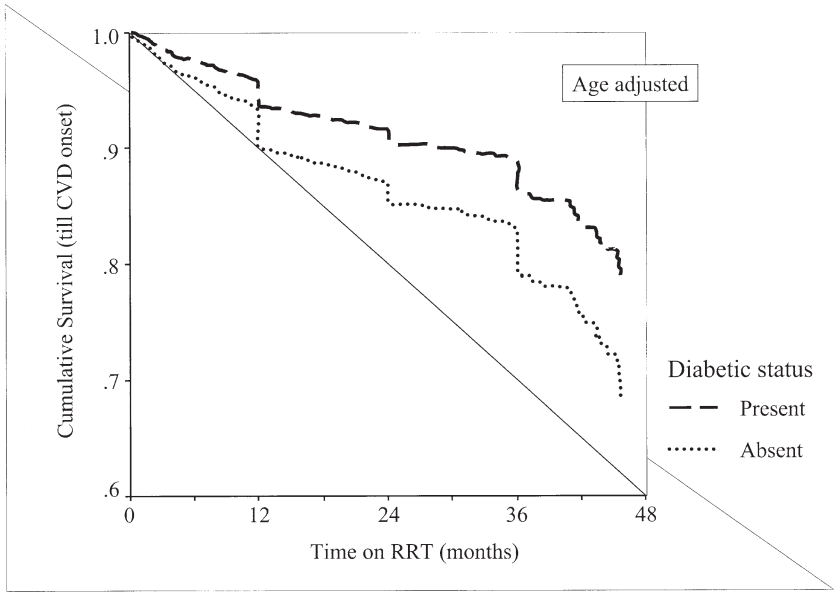

Figure 2 Risk for the development of de novo cardiovascular disease according to the presence or absence of diabetes mellitus at the start of dialysis. Data are obtained from 4,139 patients without cardiovascular disease who started dialysis between 1994 and 1997 in Lombardy. Relative risk = 1.56, 95% confidence interval = 1.19-2.05, $P < .043$. Diabetic staus: - - -, present; · · · , absent. Data from the Registro Lombardo Dialisi e Trapianto.

ease, 6% had peripheral vascular disease, and 48% had LVH, the latter being significantly more frequent in Northern European patients than in Southern European and Asiatic patients.[11] These findings suggest that factors leading to the development of cardiovascular abnormalities begin to operate very early in the progression of CKD, well before patients reach ESRD.

Cardiovascular Risk Factors in CKD

CKD patients are exposed to a number of cardiovascular risk factors, also including the so-called traditional ones, which are observed with particular frequency among patients with CKD compared with the general population. Indeed, it has been shown that the prevalence of all of the major traditional cardiovascular risk factors other than smoking (ie, hypertension, diabetes, dyslipidemia, hyperhomocysteinemia, and overweight) is significantly higher in patients with even mild renal failure than in those with normal renal function.[12] Two circumstances may be responsible for this finding: CKD itself may in many cases lead to the development or to a worsening of traditional cardiovascular risk factors (in particular, the role of renal impairment must be considered in the development of secondary hypertension), and CKD may be a consequence of one or more underlying cardiovascular risk factors; regarding the latter point, it is worth noting the increasing importance of hypertension and diabetes mellitus as primary causes of ESRD worldwide.

Besides traditional cardiovascular risk factors, CKD patients also are exposed to a number of conditions that are specific to CKD and that significantly contribute to the development of cardiovascular disease as well, also explaining why patients with CKD are exposed to a significantly higher annual mortality rate than patients with normal renal function, even after adjustment for blood pressure levels and other traditional cardiovascular risk factors.[13] These CKD-related cardiovascular risk factors include hemodynamic overload caused by plasma volume expansion and arteriovenous fistula, anemia, disorders of calcium-phosphate metabolism, electrolyte imbalances, chronic inflammation, increased oxidant stress, hypercatabolism, and even uremia, which is characterized by the accumulation of potential cardiodepressant toxins and an acceleration of both inflammatory and oxidant processes. Once patients start dialysis, their cardiovascular risk profile is increased by the exacerbation of pre-existing cardiovascular abnormalities owing to the decrease in the residual renal function. In addition, they are exposed to a number of additional risk factors related to the dialytic procedure itself, such as hemodynamic stresses caused by intra- and interdialytic changes in cardiac filling and fluctuations of blood pressure, rapid changes in serum electrolyte levels, bioincompatibility of membranes, and dialysate impurity.

Considering the multiple cardiovascular risk factors operating in CKD patients, as well as the crucial role of their cardiovascular conditions on long-term outcome, it is mandatory that all available interventions aimed at the correction of all the modifiable risk factors potentially leading to the development of cardiovascular disease are performed as early as possible in the progression of the disease.

Anemia and Cardiovascular Outcome

Anemia is a frequent complication in CKD patients, even in the earlier stages of the disease.[14,15] Although it can be treated effectively through the administration of recombinant human erythropoietin, a great proportion of patients reach ESRD in an anemic state, as documented by several large-scale observational studies.[16,17]

The importance of anemia as a risk factor for cardiovascular morbidity and mortality, as evidenced by several large-scale observational studies,[16,18-22] is substantially caused by the important role of anemia in the pathogenesis of LVH that negatively affects the outcome of these patients.[23] Indeed, anemia, together with hypertension, is thought to play a prominent role in this context.[10,24,25]

If anemia is a potentially modifiable risk factor for the development of LVH, then its correction is expected to lead to a substantial improvement in the cardiovascular status of CKD patients. Some small studies have shown that a partial regression of LVH can be obtained after the normalization of anemia if this is performed in the conservative phase of CKD.[26,27] The beneficial cardiac effects of early correction of CKD-related anemia recently have been confirmed by Silverberg et al,[28] who studied 179 CKD patients with moderate to severe congestive heart failure (New York Heart Association classes III and IV) and found that treating anemia so as to achieve and maintain a target hemoglobin level of 12.5 g/dL led to an improvement in cardiac functional status and in symptoms of heart failure. However, the Canadian Normalization of Haemoglobin Study, which was performed in hemodialysis patients, found that when LVH is well established it could not be modified significantly even after a complete correction of the anemic sate.[29] Therefore, it is reasonable to believe that some benefit on the reduction of LVH can be expected from anemia correction only if this is performed as soon as possible in the course of CKD. In any case, further studies with longer follow-up periods are needed before drawing a definitive conclusion.

What target hematocrit level should we aim for still is another open question. Although the current guidelines recommend a target hemoglobin level of 11 to 12 g/dL (hematocrit 33% to 36%),[30,31] which means maintaining a partially anemic state, it still is unclear whether further correction of anemia in CKD patients to reach a complete normalization of hemoglobin levels could lead to additive cardiac advantages in these patients, also considering the higher costs[32] and the potential adverse effects (cardiovascular events, hypertension, thrombosis of the vascular access) of such intervention. The United States Normal Haematocrit Trial showed a trend toward higher mortality and higher incidence of vascular access thrombosis in hemodialysis patients who were ran-

domized to hematocrit normalization than in those assigned to only partial correction of anemia,[33] but the baseline characteristics of the patients enrolled in the study, a large percentage of them being affected by severe cardiac heart failure or diabetes or having grafts as vascular access, could have contributed significantly to these results. Also, in the Canadian Normalization of Haemoglobin Study, which was performed in patients with a less severe degree of cardiac damage, changes in the left ventricular index were similar in patients randomly assigned to achieve a normal or a low target hemoglobin level.[29] However, a mild correlation between the degree of LVH changes and the level of hemoglobin achieved was observed in patients with concentric LVH enrolled in this study,[29] and even in the United States Normal Haematocrit Trial a positive trend was found in patients' outcome with higher achieved hematocrit levels in both randomization groups, although such an observation could be conditioned significantly by selection biases.[28] We also should bear in mind that complete correction of anemia also can be effective in improving patients' quality of life in selected categories of patients (in particular, patients without severe cardiovascular disease), without increasing the risk for death and vascular access thrombosis.[29,34,35] As a consequence, in our current state of knowledge, the best strategy for the management of renal anemia seems to consist of tailoring the target hemoglobin concentration to individual characteristics, mostly taking into consideration the presence of cardiovascular comorbidities, but only the results of other ongoing studies analyzing the target hemoglobin concentration in CKD patients, in particular the international Cardiovascular Reduction Early Anemia Treatment with Epoetin β study, will give a definitive answer to this issue.

Calcium-Phosphate Disturbances and Cardiovascular Outcome

Since the retrospective study by Block et al,[36] it has become evident that calcium-phosphate disorders, and in particular high levels of serum phosphate, which are present in about one half of patients undergoing dialysis, significantly contribute to the development of cardiovascular disease, leading to increased overall and cardiovascular mortality. The link between hyperphosphatemia and cardiovascular disease comes from the observation, recently confirmed by Raggi et al[37] in a cross-sectional analysis of 205 maintenance hemodialysis patients, that high serum phosphate levels are an independent risk factor for vascular calcification, in particular coronary artery calcification, which in turn is associated with clinically significant atherosclerotic cardiovascular disease.

Orally administered calcium-containing salts have been the most popular pharmacologic device for the treatment of hyperphosphatemia in CKD patients so far, but the observed association between calcium intake and coronary artery calcification[38] has raised concerns as to the potential detrimental effects of these drugs, leading to the search for new calcium-free and aluminum-free phosphate binders. Particularly promising results have been found with Sevelamer (Genzyme, Cambridge, MA), a novel, nonabsorbed, calcium-free, phosphate binder that has been reported to significantly slow the progression of cardiovascular calcifications in both experimental models and hemodialysis patients.[39,40] However, further studies with harder end-points are needed to determine whether the reduction in vascular calcification actually translates into lower long-term cardiovascular morbidity and mortality.

Other Cardiovascular Risk Factors

Although lipid abnormalities seem to contribute to the high cardiovascular mortality and morbidity of the CKD population,[41] the benefit of correcting lipid disorders to prevent cardiovascular events in CKD patients has not yet been validated by the results of intervention trials. Even the guidelines issued by the European Joint Task Force and the National Cholesterol Education Program Expert Panel for the correction of lipid disorders in CKD patients[42] are simply based on the assumption that CKD patients have to be considered at high risk for cardiovascular disease and therefore should be treated accordingly, but no clinical trials have confirmed the effectiveness of such recommendations. For these reasons, the results of some ongoing large-scale intervention trials studying the effects of lipid-lowering treatments in CKD patients, in particular the Determination of Cardiovascular End-points in Non–Insulin-Depenedent Diabetes Mellitus Dialysis Patients trial,[43] urgently are awaited so as to have the chance of defining more evidence-based recommendations.

Hyperhomocysteinemia is associated strongly with CKD, being present from the earliest stages of the disease and becoming prevalent in almost 90% of ESRD patients.[44] Although plasma homocysteine levels can be decreased effectively in CKD patients by means of folic acid and vitamin B supplementation, similar to lipid-lowering interventions, there is no evidence so far of a positive impact of these therapies on patients' cardiovascular morbidity and mortality.

Because of multiple potential causes related to renal impairment and to the dialytic procedure itself, a considerable proportion of CKD patients, particularly those with ESRD, are in a state of chronic systemic inflammation.[45] Considering the observed association between serum concentrations of inflammatory markers (in particular, C-reactive protein) and cardiovascular mortality in ESRD patients,[46-48] increasing attention has been paid to this issue. Nevertheless, there are as yet no valid recommendations regarding how to manage chronic inflammation in CKD patients other than optimizing the hemodialytic procedure by using biocompatible membranes and ultrapure dialysate or treating basic comorbidities contributing to inflammation (such as infections or cardiovascular disease). The safety and effectiveness of anti-inflammatory devices in decreasing CKD patients' cardiovascular outcomes have not been evaluated yet by prospective randomized studies.

Finally, CKD patients are subjected to enhanced oxidative

stress, as a result of increased pro-oxidant activity and decreased antioxidant systems.[49] This is thought to contribute to the excess cardiovascular morbidity and mortality in this population. Indeed, there is growing experimental and clinical evidence that oxidative stress may be implicated in the pathogenesis of several complications of ESRD, including accelerated atherosclerosis,[50] although no prospective epidemiologic studies are available to date to confirm the existence of a link between the extent of oxidative stress and patient outcome. These observations have led to increasing emphasis being given to CKD-related oxidative stress, also considering that it may be a new target for therapeutic interventions aimed at preventing the occurrence of cardiovascular events in CKD patients. Nevertheless, in our current state of knowledge, only one intervention study, the Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease trial, which prospectively investigated the effect of supplementing a cohort of 196 hemodialysis patients with a history of cardiovascular disease with an anti-oxidant device (a daily oral dose of vitamin E), found a significant improvement in patients' cardiovascular outcomes.[51] However, these results are not conclusive regarding the clinical benefit of antioxidant interventions in reducing cardiovascular disease in CKD patients and still are insufficient for giving therapeutic recommendations.

Conclusion

Because of the very high prevalence of a number of cardiovascular risk factors, CKD patients experience an excess of cardiovascular morbidity and mortality compared with the general population. The presence of many of these risk factors, even in the early stages of renal impairment, suggests that any effort should be made by the nephrologist to detect and possibly treat any modifiable risk factor as soon as possible in the course of the disease. Particular attention must be paid to the correction of 2 complications of CKD, namely anemia and calcium-phosphate disorders, because these interventions have proven to be effective in reducing the burden of cardiovascular disease in CKD patients in several clinical trials. A number of additional and emerging cardiovascular risk factors are active in CKD patients and could represent further potential targets for therapeutic strategies, but a clear evidence of the ability of these interventions to actually decrease the occurrence of cardiovascular events in this population still is lacking. Only with the results of further large-scale, prospective, randomized trials will it be possible to claim that the available opportunities for the management of the cardiovascular risk in CKD patients are more than those used until now.

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