MÆDICA - a Journal of Clinical Medicine

EDITORIALS

What do we have to learn from recent studies in *dialysis patients?*

Nicoleta MARDARE, MD; Paul GUSBETH-TATOMIR, MD;
Adrian COVIC, MD PhD

Dialysis and Transplantation Center, „Dr. C.I. Parhon" University Hospital and University of Medicine and Pharmacy „Gr.T. Popa", Iasi, Romania

ABSTRACT

Chronic kidney disease (CKD) has been recently recognized as an important public health issue. The most advanced form of CKD, end-stage renal disease (ESRD), is associated with an impressive cardiovascular (CV) mortality, comparable with the worst malignancies. For many years, most data on therapy of CV therapy in dialysis patients were derived from observational studies or were extrapolated from the general population. However, ESRD patients may have a particular CV profile, as not just classical CV risk factors, but also uremia-related risk factors contribute to the high CV morbidity. Therefore, the nephrological community has focused in the last decade on randomized controlled studies examining the effect of various drugs on outcome in dialysis patients. These studies are comprehensively reviewed by the authors. Unfortunately, most of these studies are negative or inconclusive, suggesting that aggressive cardiac and vascular protective medication should be used in CKD long before reaching end-stage renal disease. Another interesting approach is the multiple intensive therapeutic intervention in dialysis patients, addressing all known CV risk factors in this population. Until now, this approach has generated conflicting data and is generally difficult to implement in the daily clinical practice. Thus, more appropriately designed studies in ESRD patients are mandatory in the near future.

Key words: anemia, cardiovascular disease, chronic kidney disease, end-stage renal disease, hemodialysis, reverse epidemiology, therapy, trials

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem, with adverse outcomes of kidney failure, cardiovascular disease (CVD), and premature death. A simple definition and classification of kidney disease is necessary for international development and implementation of clinical practice guidelines. In a narrow sense, CKD is defined as glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 with or without evidence of kidney damage, for 3 months or more, irrespective of cause (1).

Address for correspondence:
Adrian Covic, MD, PhD, Professor of Nephrology, „C.I. Parhon" University Hospital, 1st No. 50 Carol Blvd., Iasi, Zip code 700503, Romania
email address: acovic@xnet.ro

Severe, stage 5 CKD (referred also as end-stage renal disease – ESRD), defined as a GFR < 15 ml/min/1.73m^2, which is often related to diabetes or hypertension, is a serious medical and economic public health problem throughout the world. At the end of 2004, some 1,783,000 people worldwide were undergoing treatment for ESRD – 1,371,000 (77%) were on dialysis treatment and 412,000 (23%) were living with a functioning renal transplant (2). Based on an extrapolation of the 2004 patient numbers and 2003–2004 growth rates, in US alone, the number of dialysis patients will approach 2 million by the year 2010. Furthermore, according to these facts and taking the different regional growth rates into consideration, there will be a significant change in the regional distribution of patients, with around 50% of all dialysis patients in 2010 being treated in countries outside the USA, the EU and Japan, as opposed to about 40% in 2004 (3). The development and the size of national renal replacement therapy (RRT) programmes are variable from country to country, since they have been recognized to be dependent on political, economic and socio-cultural conditions. In Romania, there is still a explosive development of the dialysis programe, with a population of 5,447, i.e. a median prevalence of 250 treated end-stage renal disease (ESRD) cases p.m.p in 2003 (4). Age at RRT initiation significantly increased, but the proportion of patients over 65 years old is below the mean reported by the Euro-DOPPS survey in Western Europe (47%). Significant trends were also observed in ESRD etiology: doubling of diabetes and nephroangiosclerosis cases from 1996 to 2002 (4). Reliable and up-to-date information on ESRD patient numbers and treatment outcomes as well as optimizing treatment of chronic kidney disease (CKD) and establishing meaningful, evidence-based strategies for prevention are indispensable duties of any regional and national healthcare authority.

Cardiovascular (CV) medicine was for a long period of time the "queen of medicine". The *Framingham Heart Study* practically set the basis for a new approach to clinical practice: a central role for cardiovascular risk factors and the evidence based medicine. After that, a series of large, prospective, randomized trials based on fatal and nonfatal events in primary and secondary prevention were designed and carried out during the late '70s, '80s and '90s. The results of these trials fundament today's therapeutic guidelines in cardiovascular medicine. Most of these outcome trials have been included to meta-analyses, either to arrive to more precise and general conclusions or to answer questions on subgroups which could be not addressed in individual studies

In the last decade a similar evolution was seen in nephrology. Starting with the year 1999 the results of a series of prospective trials in dialysis patients have been published changing and challenging current clinical practice. It is no secret that the rather surprising general trend of these efforts has been "negative" with few exceptions. One after the other the intervention arms of these randomized controlled trials (RCT) failed to prove the expected effect, somehow germinating a pessimistic mood in the renal community. However, right from the start, a major difference is apparent between cardiovascular and renal medicine: the complexity of the studied population and the size of these trials. Nevertheless, it is now time to critically assess how the results of these studies impacted on our daily practice and on our approach to plan/design future studies in nephrology. We are going to analyze the result of the major RCT:

a. related to the overall dialysis efficiency to decrease the entire burden of uraemic toxins, regardless of their pathogenic impact (the "indiscriminate approach");
b. related to the major mortality cause – vascular pathology (accelerated atherosclerosis, vascular calcifications, arteriosclerosis and left ventricular hypertrophy – the "most plausible suspect" approach).

a. Classic decrease of uraemic toxins: *dialysis dose and size of the molecules removed*

Two treatment-related factors implicated in the substantial mortality and morbidity seen in patients undergoing maintenance hemodialysis are the dose of dialysis delivered and the size of molecules removed. The *National Cooperative Dialysis Study*, the first randomized trial on dialysis dose and morbidity, established a beneficial effect of an increased dialysis dose on morbidity but at dialysis doses well below the current standard and in patients with substantially fewer coexisting conditions than found in the present population of patients

undergoing hemodialysis (5). Subsequent observational studies have suggested that membranes with high porosity or flux, which clear larger solutes such as beta2-microglobulin (molecular mass, 11,900 D), are associated with improved outcomes. Therefore, the HEMO (Hemodialysis) study was the first randomized clinical trial designed to determine whether increasing the dose of dialysis or using a high-flux dialyzer membrane improves survival or morbidity among patients undergoing hemodialysis (6).

Eligible patients were randomly assigned in a 1:1 ratio with a two-by-two factorial design to either a standard-dose or a high-dose goal and to dialysis with either a low-flux or a high-flux dialyzer. In the study group, the strongest predictors for death were age, base-line serum albumin level, coexisting conditions, race, and years of dialysis.

Neither the differences between the two dose groups nor the differences between the two flux groups were significant. After adjustment for base-line factors, the high-dose group had a risk of death that was only 4% lower (95% CI=10–16; P=0.53) than that of the standard-dose group, and the high-flux group had a risk of death that was 8% lower (95% CI=5–19; P=0.23) than that of the low-flux group. The effects of the dose and flux interventions were similar at both levels of the other variable (P for interaction=0.30). The only significant interactions were between the dose intervention and gender (women in the high dose group had 19% lower risk of death than standard group) and between the flux intervention and dialysis duration (patients in the high flux group with more than 3.7 years on dialysis had a 32% decreased risk of death than the low flux group). In the end, the conclusion was that among patients undergoing maintenance hemodialysis who were receiving thrice-weekly treatments lasting 2.5 to 4.5 hours each, neither a higher dose of dialysis nor the use of high-flux membranes significantly improved survival or reduced morbidity. This lack of effect was found despite a clear separation in fractional urea and beta2-microglobulin clearances between the treatment groups.

For peritoneal dialysis (PD) patients, small-solute clearance targets have often been established on the basis of the tacit assumption that peritoneal and renal clearances are equivalent and therefore additive. However, many studies that examined the relationship between small-solute clearances and mortality rates in PD patients noted that patient survival directly correlated with renal clearance, the contribution of peritoneal clearance remaining unclear. ADEMEX (*ADEquacy of PD in MEXico*) (7) was the first prospective, randomized, controlled, interventional trial to examine the effects of increased peritoneal small-solute clearances (beyond a standard minimal prescription) on survival for patients undergoing PD. A total of 965 subjects in 24 centers were randomly assigned to the intervention or control group (in a 1:1 ratio). Despite differences in small-solute clearances patient survival was similar for the control and intervention groups, as indicated by intention-to-treat (ITT) analysis, with a RR of death (intervention/control) of 1.00 (95% CI, 0.80 – 1.24). In additional ITT analyses, mortality rates for the two groups remained similar when patients within each group were stratified according to a variety of measures known to be associated with patient survival (e.g., age, diabetes mellitus, serum albumin levels, nPNA values, and anuria).

In conclusion, the available evidence does not support a net beneficial role on patient survival for increasing the dialysis dose (PD and HD). Most plausible explanations: either the evaluated increase in dose was not sufficient or nondialysable toxins are more important in a patient where frequently damages are already irreversible.

b. Targeting cardiovascular pathology *(accelerated atherosclerosis, dyslipidemia, hyperhomocysteinemia, arteriosclerosis and vascular calcifications)*

Atherosclerotic cardiovascular disease is a significant cause of morbidity and mortality for patients with chronic renal failure. A number of factors, including age, hypertension, hyperlipidemia, and diabetes, have been found to be strongly associated with an increased incidence of atherosclerosis in the general population. Some of these conditions have a higher prevalence in patients with ESRD. In the general population, after the emergence of Framingham Study results, numerous trials have been conducted in primary and secondary prevention of atherosclerosis. The results were encouraging

showing a significant benefit on mortality from specific interventions such as: life style and dietary intervention, blood pressure lowering, lipid lowering therapy, inflammation treatment (8).

LIPID LOWERING THERAPY

Primary and secondary prevention trials have documented substantial cardiovascular benefits from lipid lowering strategies, particularly use of statins (9). Different statins at a range of doses reduced total cholesterol by 17–35% and LDL-cholesterol by 24–49% from baseline. The 4D (*Die Deutsche Diabetes Dialyse*) Study (10) was an investigator-initiated, prospective, randomized, placebo-controlled study of patients with type 2 diabetes mellitus receiving hemodialysis designed to answer two questions: what is the benefit of statins in hemodialyzed diabetic patients and what is the safety profile of the drug in this special population. A total of 1255 subjects were randomly assigned to double-blind treatment with either atorvastatin (619) or placebo (636) between 1998 and 2002 and were followed until their final visit in march 2004. The cumulative incidence of the primary end point was 12.6 % at one year and 31.9 % at three years in the atorvastatin group, as compared with 11.2 % and 30.5 %, respectively, in the placebo group. The relative risk reduction afforded by active treatment, as compared with placebo, was 8 % (HR=0.92; 95 % CI 0.77 to 1.10; P=0.37). In the 4 D Study, atorvastatin (20 mg/day) lowered LDL cholesterol levels by 42 %, to 72 mg/dl, close to the target value recommended by the Third Adult Treatment Panel of the NCEP for persons at very high risk of cardiovascular disease. Despite the high rate of cardiovascular events and the pronounced LDL cholesterol–lowering activity of atorvastatin, a significant reduction in the incidence of the composite primary end point was not achieved. Of significance, more cases of fatal stroke occurred in the atorvastatin group (27) than in the placebo group (13).

Some of the explanations proposed by the study investigators: different pathogenesis of vascular events in uraemic, diabetic patients; the presence of additional pathogenetic pathways, different from the traditional cardiovascular risk factors; structural abnormalities that cannot be reversed despite a significant decrease in LDL cholesterol. As a conclusion, the study suggests that the benefit of atorvastatin is limited (or even dangerous) when intervention with statins is postponed until patients have reached end-stage renal disease.

Conventional CV risk factors, such as hypertension and hyperlipidemia, are common also in transplant recipients. *Assessment of Lescol in Renal Transplantation* (ALERT) is the largest published interventional trial in renal transplantation and the first large-scale clinical trial to address CV complications in this population (11). This was an investigator-led, randomized, double-blind, parallel-group study that compared fluvastatin (Lescol^{R}; 40 to 80 mg/d) with placebo in 2,102 patients followed up for a minimum of 5 and a maximum of 6 years. After a mean follow-up of 5.1 years, fluvastatin lowered LDL cholesterol concentrations by 32%. Risk reduction with fluvastatin for the primary endpoint (RR 0.83; 95% CI 0.64-1.06; p=0.139) was not significant, although there were fewer cardiac deaths or non-fatal MI (RR 0.65; 95% CI 0.48-0.88; p=0.005) in the fluvastatin group than in the placebo group. Coronary intervention procedures and other secondary endpoints did not differ significantly between groups. Overall effects of fluvastatin were similar to those of statins in other populations. There are not yet other statin trials in CKD, and we are waiting with interest the results of the SHARP (*Study of Heart and Renal Protection*) study.

SERUM HOMOCYSTEINE LEVEL

High serum total homocysteine (tHcy) is an established risk factor for cardiovascular disease in the general population. In ESRD, mean homocysteine levels are commonly elevated, and the role of homocysteine as a cardiovascular risk factor has been confirmed by some prospective studies (12). Consequently, Wrone et al (13) designed a trial to respond to one very important question: "does supplementation with a multivitamin containing folic acid in 5-mg or 15-mg doses reduce a composite end point of mortality and cardiovascular events over 3 yr compared with standard therapy (1 mg of folic acid)?". In this trial 510 pts were included, with a mean age of 60 y, and a large proportion of diabetic patients. They were randomized to receive 1 mg, 5mg or 15 mg of folic acid for a median duration of treatment of 24 months. In the end, the analysis

showed disappointing results: there was no difference in the composite end-point at 24 months (43.7% in arm 1, 38.6% in arm 2, 47.1% in arm 3; log-rank P = 0.47) among the treatment arms. Similarly, there was no difference among the treatment arms in total survival or cardiovascular events when analyzed separately. The lack of difference in outcomes between the groups could have multiple explanations: tHcy reduction is beneficial, but the study is underpowered to detect differences due to small effect size and due to strong confounding of associations; tHcy is not a causative agent (or plays a very minor role) in this group of patients who tend to suffer from multiple, advanced chronic diseases.

MINERAL METABOLISM AND VASCULAR CALCIFICATION IN ESRD

Disorders of mineral metabolism and vascular calcifications are common among ESRD patients. Numerous observational studies demonstrated a strong association between abnormalities in mineral metabolism and all-cause mortality (14) mainly through the development of cardiovascular disease (CVD) and cardiovascular mortality (15). Furthermore, some recent much debated studies suggested that the choice of phosphate binder may be relevant in terms of outcome (16). Asmus et al (17) compared the effects of a calcium with a non-calcium phosphate binder on arterial calcification in 72 dialysis patients followed for 2 years. Despite similar calcium phosphate product, patients receiving CC had significantly increasing in coronary artery (CC median 484, P<0.0001, SEV median 37, P = 0.3118, between-group P = 0.0178) and aortic (CC median 610, P = 0.0003, SEV median 0, P = 0.5966, between-group P = 0.0039) calcification scores. This suggests that sevelamer, a non-calcium phosphate binder could have a beneficial effect on vascular calcification scores on long term administration.

Sevelamer can have a beneficial effect on calcification also in the incident hemodialysis patients. Block et al (18) studied the calcification scores in 109 incident patients on HD, randomly assigned to sevelamer or calcium-containing phosphate binders; follow-up 18 months. At baseline, 63% of sevelamer treated and 69% of calcium treated patients had evidence of coronary calcification. Subjects with a coronary artery calcium score (CACS) > 30 at baseline showed progressive increasing in CACS in both treatment arms (P < 0.05 for each time point in both groups). Subjects treated with calcium containing phosphate binders showed more rapid and more severe increases in CACS when compared with those receiving sevelamer hydrochloride: median absolute increase in CACS at 18 months was 11-fold greater in the calcium treated group compared to the sevelamer-treated group (P = 0.01 at 18 months).

The *Dialysis Clinical Outcomes Revisited* (DCOR) trial was designed to be the largest outcomes study ever conducted in the hemodialysis population. The three-year trial involving more than 2,100 patients compared the difference in mortality and morbidity outcomes for patients receiving sevelamer hydrochloride with those using calcium-based phosphate binders. It is significant that in the preliminary general analysis, the patients who used sevelamer experienced only a 9% reduced risk of death from all causes relative to patients using calcium-based phosphate binders, result not statistically significant (p=0.30); the same situation for the secondary endpoints. Sevelamer use resulted in the strongest clinical benefit in two groups of patients: those who were treated for two years or more (all cause mortality reduced by 34% in pts using sevelamer; p=0.02), and those who were 65 years of age or older (22% reduction in all cause mortality; p=0.03). Although this was a pre-specified subgroup analysis the result only improved the beliefs of both camps: supporters of sevelamer and those still considering that calcium-based phosphate binders should still have a central role in our daily management.

LEFT VENTRICULAR DYSFUNCTION

Decreased renal function has consistently been found to be an independent risk factor for cardiovascular (CV) disease outcomes and all-cause mortality in a large spectrum of CV patients, including those with left ventricular systolic dysfunction and chronic heart failure (CHF). In terms of clinical application, renal function may potentially be a stronger predictor of clinical events than left ventricular ejection fraction (LVEF). The CHARM (*Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity*) study (19) provided the evidences for the importance of renal

function as prognostic factor for survival. Both a reduced GFR and lower LVEF were found to be significant independent predictors of worse outcome after adjustment for major confounding baseline clinical characteristics."

Abnormalities in left ventricular (LV) size and function are common and may be encountered in 70-80% of the incident dialysis patients, as they start renal replacement therapy (20). These alterations develop early in the course of renal disease (e.g. eGFR ~ 60 ml/min) and their prevalence progresses in parallel with the decline in renal function (21). Similar to the general population, left ventricular hypertrophy (LVH) is a powerful predictor of mortality in dialysis patients (22) and its regression has been associated with a lower incidence of major cardiovascular events and a better survival rate (23). Development of LVH in chronic kidney disease (CKD) patients is multifactorial; the principal etiologic factors are the high LV afterload and anemia (24).

Anemia is a frequent complication of chronic kidney disease (CKD) and is primarily due to failure of erythropoietin production to respond to decreased hemoglobin concentration. The onset of anemia during the progression of CKD is variable, but it is common after serum creatinine reaches 1.5 mg/dl and increases in prevalence with decreasing creatinine clearance. (25) A recent report by al-Ahmad *et al*. (26) found that CKD and anemia are independent risk factors for mortality among patients with heart failure due to left ventricular dysfunction. This report is of particular interest given that the prevalence of heart failure was 33% among new ESRD patients.

In ESRD patients in dialysis anemia is a easy treatable condition with erythropoiesis-stimulating agents (ESA's) and partial correction of anemia results in regression of LVH. Thus, a series of studies investigating the impact of hemoglobin (Hb) normalization have been performed.

Besarab et al (27) were the first to examine the benefits and risks of a normal haematocrit (Ht) in HD patients with cardiac disease. Study group included 1233 patients with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 patients were assigned to achieve and maintain a haematocrit of 42 %, and 615 were assigned to maintain a haematocrit of 30 % throughout the study. The median duration of treatment was 14 months. Of note baseline characteristics of the patients revealed a high proportion of diabetics and the predominance of synthetic grafts for vascular access. The relative risk for the primary outcome (death or first nonfatal MI) was 30% higher in the normal haematocrit group and the rates of access loss were significantly higher. Although the difference in event-free survival between the two groups did not reach the prespecified statistical stopping boundary, the study was halted, suggesting that in patients with clinically evident congestive heart failure or ischemic heart disease who are receiving hemodialysis, administration of epoetin to raise their hematocrit to 42% should be avoided.

Foley et al. (28) enrolled 146 hemodialysis patients with either concentric left ventricular hypertrophy (LVH) or LV dilation who were randomly assigned to receive doses of epoetin to achieve hemoglobin levels of 10 or 13.5 g/dl; with a follow-up period of 48 weeks. The higher hemoglobin target failed to induce regression of pre-existing concentric LVH or dilatation although secondary outcome analysis suggested that higher hemoglobin levels could prevent de novo left ventricular. Therefore in 2005 the same group published a similar study in 596 incident HD, free of symptomatic CVD and LV dilatation (29). In this randomized, double-blind study, lower (9.5 to 11.5 g/dl) and higher (13.5 to 14.5 g/dl) hemoglobin targets were generated with epoetin alpha over 24 wk and maintained for an additional 72 weeks. Percentage changes in LVVI between baseline and last value were similar (7.6% in the higher and 8.3% in the lower target group) as were the changes in left ventricular mass index (LVMI) (16.8 versus 14.2%). The authors concluded that normalization of hemoglobin in incident hemodialysis patients did not had a beneficial effect on cardiac structure, compared with partial correction.

Hemoglobin normalization studies have been developed also for CKD patients not on dialysis. Roger et al. (30), conducted a study on 155 patients with CKD (creatinine clearance 15 to 50 ml/min), randomized to receive epoetin alpha as necessary to maintain hemoglobin level between 12 and 13 g/dl (group A) or between 9 and 10 g/dl (group B). On an ITT analysis, the changes in LVMI for the groups during the 2-yr period were not significantly different (2.5 ± 20 g/m^2 for group A versus 4.5 ± 20 g/m^2

for group B, P = NS). Similar results were recently reported by the CREATE study (*Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin Beta*).

Results from these studies and other longitudinal observations suggest that hemodialysis patients with "uremic cardiomyopathy" exhibit an inexorable disease progression, with a very high mortality and morbidity despite the routine pharmacologic therapy and the optimization of the dialysis regimen. However, if validated by larger trials, a promising approach (derived from larger cardiovascular trials) could be implemented in patients with ESRD. A group of 132 hemodialysis patients with dilated cardiomyopathy and a left ventricular ejection fraction 35%, symptomatic for heart failure for at least one year, were followed under carvedilol therapy by Cice and coworkers (31). The cumulative two-year mean survival time was 20.4 months in the carvedilol group and 18.3 months in the placebo group (log-rank, 8.58; p 0.005). Surprisingly, 12-month mortality rate was 0% in the carvedilol group versus 5.2% in the placebo group (p = NS), but it increased, respectively, to 51.7% and 73.2% (p = 0.01) at two-year follow-up.

As a summary, despite the fairly large number of patients included in these RCT, neither increasing dialysis dose, nor targeting major cardiovascular risk factors such as dyslipidemia, hyperhomocysteinemia, anemia and calcium phosphate abnormalities did exert a marked beneficial impact on cardiovascular and all cause mortality in dialysis patients. The rather disappointing conclusion is that in dialysis population all intervention designed to target the classical risk factors and optimize the dialysis treatment are ineffective to tackle the high morbidity and mortality, or the isolated benefits are very small, not reaching statistical significance to be selected as a single viable alternative for lowering the cardiovascular risk in this special population group.

Thus we should return to the initial, central question: why the (high) mortality in ESRD patients on HD can not be reduced? The answer to this question is clearly complex but could be the result of:

- **i)** particular demographics of the ESRD population;
- **ii)** different influence of classical, known risk factors the so called "reverse epidemiology";
- **iii)** the fact that we are not targeting the right toxin or the single intervention approach is not the correct one; iv) (most probably of all) that the single intervention paradigm is not applicable to our complex population.

i. Changing demographics of the HD population

In the early 80's the mean age of the patients on HD in Europe was 52 years and less that 5% were diabetics, with few with other comorbidities. Subsequent liberalization of acceptance rates onto dialysis programs resulted in a significant shift in the dialysis population: patients are older (mean age over 60 years); more diabetics (in USA the figure approaches 50%); many with important non-renal comorbidities, particularly a high percentage of chronic heart failure (over 30% of the incident HD patients in America) (2).

ii. The reverse epidemiology paradigm

Observational studies in general population revealed a linear relationship between cardiovascular risk factors and mortality in the general population. In maintenance hemodialysis patients, associations between demographic, clinical and laboratory values and mortality, including cardiovascular death, are significantly different and, in some cases, in the opposite direction of those derived from the general population (32, 33).

A significant portion of this reverse epidemiology may be accounted for the overwhelming effect of the malnutrition-inflammation complex syndrome (MICS). Since two thirds of HD patients die within 5 years of initiation of dialysis treatment, traditional cardiovascular risk factors such as obesity, hypercholesterolemia and hypertension cannot exert a long-term deleterious impact, and instead, their short-term beneficial effects on MICS provides a survival advantage. (34). Additionally, Liu et al. (35) studied 823 patients on hemodialysis that were classified by the presence/ absence of inflammation and followed for a mean of 2.4 years. In the presence of inflammation, the increase in serum cholesterol was associated with decrease mortality (11% decreases in mortality for a 40mg/dl increase in total cholesterol). In contrast, serum cholesterol was associated with a significant 32% increase in all

cause mortality in the group without inflammation. The data suggests that the inverse association of total cholesterol level with mortality in dialysis patients is in fact due to the cholesterol-lowering effect of systemic inflammation and malnutrition, not to a protective effect of high cholesterol concentrations.

A similar association has been recently suggested by Suliman et al for the serum homocysteine (36). The hypothesis that total plasma total homocysteine (tHcy) level is an indicator of poor outcome has been evaluated in 317 ESRD patients incident on HD, followed for 66 months. After adjusting for age, gender, glomerular filtration, cardiovascular disease, plasma folate, total cholesterol and diabetes mellitus, the all-cause and CV mortality still tended to be high for patients with low tHcy. Adding nutritional and inflammation markers (Body mass index, SGA, serum creatinine, serum albumin and CRP), a low tHcy level was no longer associated with higher mortality. After adjustment for confounders including nutritional and inflammation markers, a trend towards increased death risk for high, rather than low, tHcy levels was apparent.

iii. Did we found the "real"/"major" toxin in uremia and the right intervention for it? The role of inflammation / oxidative stress.

Oxidative stress is advocated as a risk factor for atherosclerosis in general population and is augmented in dialysis patients from a variety of reasons (accumulation of oxidative metabolism product). Also it is demonstrated to be greater in hemodialysis patients with prevalent cardiovascular disease than in those without, suggesting a role for oxidative stress in excess cardiovascular disease in these patients.

Boaz and coworkers (37), run a RCT to investigate the effect of high-dose vitamin E supplementation on cardiovascular disease outcomes in hemodialysis patients with preexisting cardiovascular disease. 196 pts with previously documented cardiovascular disease on HD were enrolled and randomized to receive 800 IU/day vitamin E or matching placebo; follow-up in median 519 days. Primary endpoint was a composite variable consisting of: myocardial infarction (fatal and non-fatal), ischemic stroke, peripheral vascular disease (excluding the arteriovenous fistula), and unstable angina. The vitamin E group had a 54% risk reduction for the primary endpoint (95% CI 0.27-0.78; p=0.014). Secondary outcomes included each of the component outcomes, total mortality, and cardiovascular-disease mortality. When analyzed separately, of note, no significant differences in the secondary endpoints, cardiovascular disease, or total mortality were detected.

Acetylcysteine, a thiol-containing antioxidant, has been used successfully to ameliorate the toxic effects of ischemia-reperfusion syndromes of the heart, kidney, lung, and liver. The activity of acetylcysteine was related to its action as a free-radical scavenger or as a reactive sulfhydryl compound that increases the reducing capacity of the cell. Tepel et al. (38) recruited 134 HD patients with a mean follow-up of 14.5 mo. and randomly assigned them to receive 1,2g acetylcysteine/day or placebo. The primary end point was a composite variable consisting of cardiac events including fatal and nonfatal myocardial infarction, cardiovascular disease death, need for coronary angioplasty or coronary bypass surgery, ischemic stroke, peripheral vascular disease with amputation, or need for angioplasty. Secondary outcomes included each of the individual component outcomes. The patients in the acetylcysteine group had a risk of reaching the primary end point that was 40% lower compared with the control group (relative risk 0.60; 95% CI, 0.38 to 0.95; P=0.03); unfortunately there were no differences in secondary endpoints. These two small studies would point to the major role of increased oxidative stress and the importance of therapeutic measures addressed to counteract its effects. However many methodological issues related to the design of these small but promising trials point us to reach a definitive conclusion.

Inflammation (interrelated to insulin resistance, oxidative stress, wasting and endothelial dysfunction) can be considered an integrator of the pathogenic ways in vascular disease in hemodialysis patients. Several different inflammatory biomarkers, such as high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL6) have been shown to independently predict mortality in ESRD patients. By their close relationship to other cardiovascular risk markers as cholesterol, fibrinogen, albumin, intima-media thickness, left ventricular mass, it has been suggested that CRP is not only a marker,

but also a prognostic element of vascular disease. Recently (2006) Yilmaz et al (39) demonstrated a direct relationship between oxidative stress, endothelial dysfunction (ED) and cardiovascular outcomes in 159 nondiabetic patients with CKD. They showed that asymmetric dimethylarginine (ADMA) ($\beta = 0.228$; $P < 0.01$), erythrocyte superoxide dismutase SOD ($\beta = 0.405$; $P < 0.001$), and oxidized low-density lipoprotein levels ($\beta = 0.428$; $P < 0.001$) were related independently to brachial artery endothelium-dependent vasodilatation as a marker of endothelial dysfunction in a group of 159 patients with CKD stages 1-5 and without diabetes. Scholtze et al (40) demonstrated the metabolic and hemodynamic effects of intravenous administration of acetylcysteine (NAC) during a hemodialysis session on plasma homocysteine concentration and secondary on pulse pressure as marker of endothelial function. After NAC administration endothelial function improved by lowering plasma homocysteine. This was significantly associated with an improvement of pulse pressure and endothelial function, supporting the beneficial effects of acetylcysteine on cardiovascular morbidity in patients with end-stage renal failure.

iv. The "wrong" approach to prevention of cardiovascular disease in ESRD. Is it more effective to target all risk factors at the same time?

In all the mentioned studies the best practice and achievement of guidelines and beyond them were the standard applied to obtain the small improvements in cardiovascular mortality. Even though statistically significant, RCT's they are not very impressive in the clinical practice. First, as mentioned in many papers so far, RCT's are not the same with „real life", therefore the results of such studies should be interpreted with caution, keeping in mind that real-life patients are somewhat different of study patients. Second, one can hypothesize that all intervention can be not antagonist but additive: the sum of all effects of our interventions would result in a really significant 26% reduction in cardiovascular mortality and this may be really significant. According to this hypothesis, we should reach in our daily clinical practice all the targets set by the best practice guidelines, European and KDOQI, in order to achieve a significant difference in mortality.

The large observational trials tell us a different opinion: in real life we are far from reaching those targets. In the DOPPS trial regarding anemia (41), despite KDOQI recommendations (KDOQI gudelines recommend a mean Hb level of 11g/dl or greater), in 2002 27.5% of the dialysis population had Hb levels under the limit of 11 g/dl. Four years after the EBPG implementation only 66 % of the European hemodialysis patients had target Hb. More recent, in 2004 a new observational study was launched: the ORAMA (*Optimal Renal Anaemia Management Assessment*) trial investigates the effect of endorsing adherence to the new EBPG. A total of 739 patients from 53 centres in 8 countries were enrolled; 4/5 of patients received dialysis. The mean Hb was 11.2 g/dL. Partial results show that, although most patients (96%) received ESAs, the EBPG Hb target value of 11 g/dL was not met by half of the patients (48%).

Turning to the mineral metabolism, in the DOPPS (*Dialysis Outcomes and Practice Pattern Study*) investigation (42), a relatively modest percentage of patients fell within the guideline range for PTH (KDOQI guidelines recommendation: 150-300 pg/mL – 33.0 pmol/L) (21.4%), serum phosphate (KDOQI gudelines recommended range: 3.5-5.5 mg/dL – 1.13 and 1.78 mmol/L) (40.8%), albumin-corrected serum calcium (KDOQI gudelines: 8.4 to 9.5 mg/dL – 2.10 to 2.37 mmol/L) (40.5%), and calcium-phosphate product (KDOQI gudelines recommendation: to be maintained <55 mg^2/dL^2) (56.6%). It was rare for patients to fall within recommended ranges for all indicators of mineral metabolism: only 4.6%-5.5% of patients were within range for all 4.

So, what have we learned from the previous trials in HD patients? That no single intervention is really efficient in reducing mortality and maybe is time to try a holistic approach. We have the proof that this approach can be effective from our close friends, the diabetologists: Gaede et al. (43) applied this concept in type II diabetic patients. He compared the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for cardiovascular disease in patients with type 2 diabetes and microalbuminuria. The primary end point of this open, parallel trial was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization, and

amputation. The decline in glycosylated hemoglobin values, systolic and diastolic blood pressure, serum cholesterol and triglyceride levels measured after an overnight fast, and urinary albumin excretion rate were all significantly *greater* in the intensive-therapy group than in the conventional-therapy group. Patients receiving intensive therapy had a 53% lower risk of cardiovascular disease (HR – 0.47; 95 % CI 0.24 – 0.73), 61% lower risk of nephropathy (HR-0.39; 95% CI 0.17 – 0.87), 58% lower risk of retinopathy (HR-0.42; 95% CI 0.21 – 0.86), and 63% lower risk of autonomic neuropathy (HR-0.37; 95% CI 0.18 – 0.79).

A similar concept trial but at smaller scale and this time in HD patients demonstrates the validity of the strategy. In an interventional trial, Hampl et al (44) targeted all risk factors for chronic heart failure (CHF) at the same time, in a series of 202 consecutive HD patients. The investigators used an optimized CHF therapy, including beta-blockers (BB), ACE inhibitors and angiotensin receptor blockers (ARBs), and associated with full anemia correction by epoetin beta (hemoglobin (Hb) target males 14.5 g/dl, females 13.5 g/dl). The results were amazing: there was a significant reduction in left ventricular mass index (LVMI, 159 +/- 65 vs. 132 +/- 46 g/m2 ($p < 0.001$)), an improvement in left ventricular ejection fraction (LVEF, 60 +/- 15 vs. 66 +/- 12% ($p < 0.01$)) and in NYHA class (2.8 +/- 0.76 vs. 1.96 +/- 0.76 ($p < 0.01$)) from baseline to follow-up in the overall study population. Notably in a subgroup of 70 patients, LVMI returned to normal (169 +/- 33 vs. 114 +/- 14 g/m2 ($p < 0.001$)) after 1.4 +/- 1 years.

In conclusion, we think that a completely new large scale trial is desirable, with one arm aiming actual good practice therapy, accomplishing all actual guideline targets. In the interventional arm, a computer-led decision to accomplish the appropriate changes to reach ALL targets existent at the moment is imaginable. Supplementary, in order to target all possible risk factors, drugs to target the oxidative stress (NAC, vitamin E), optimised heart failure treatment, statins, and sevelamer may be considered in this complex therapeutic approach. It remains to look whether the nephrological community will be able to take this kind of challenge.

REFERENCES

1. **Levey AS, Eckardt KU, Tsukamoto Y et al** – Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; 67(6):2089-2100
2. www.usrds.org
3. **Grassmann A, Gioberge S, Moeller S et al** – ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. *Nephrol Dial Transplant* 2005; 20:2587-2593
4. **Mircescu G, Capsa D, Covic M et al** – Nephrology and renal replacement therapy in Romania – transition still continues (Cinderella story revisited). *Nephrol Dial Transplant* 2004; 19:2971-2980
5. **Gotch FA, Sargent JA** – A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1985; 28:526-534
6. **Eknoyan G, Beck GJ, Cheung AK et al, for the Hemodialysis (HEMO) Study Group** – Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis, *N Engl J Med* 2002; 347:2010-2019
7. **Paniagua R, Amato D, Vonesh E et al** – Effects of Increased Peritoneal Clearances on Mortality Rates in Peritoneal Dialysis: ADEMEX, a Prospective, Randomized Controlled Trial. *J Am Soc Nephrol* 2002; 13:1307-1320
8. **Steinberg D** – Thematic review series: the pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy, part V: the discovery of the statins and the end of the controversy. *J Lipid Res* 2006; 47:1339-1351
9. **Edwards JE, Moore RA** – Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomised, double blind trials. *BMC Family Practice* 2003, 4:18
10. **Wanner C, Krane V, März W, et al, for the German Diabetes and Dialysis Study Investigators** – Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; 353:238-248
11. **Holdaas H, Fellstrom B, Jardine AG et al** – Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003; 361:2024-2031
12. **Christen WG, Ajani UA, Glynn RJ et al** – Blood levels of homocysteine and increased risks of cardiovascular disease: causal or casual? *Arch Intern Med* 2000; 160: 422-434
13. **Wrone EM, Hornberger JM, Zehnder JL et al** – Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. *J Am Soc Nephrol* 2004; 15: 420-426
14. **Block GA, Hulbert-Shearon TE, Levin NW et al** – Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31:607-617
15. **Noordzij M, Korevaar JC, Boeschoten EW et al** – The K/DOQI guideline for bone metabolism and disease in CKD: association with mortality in dialysis patients. *Am J Kidney Dis* 2005; 46: 925-932
16. **Block GA, Spiegel DM, Ehrlich J et al** – Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int* 2005 Oct; 68(4):1815-1824
17. **Asmus HG, Braun J, Krause R et al** – Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. *Nephrol Dial Transplant* 2005; 20:1653-1661
18. **Block GA, Spiegel DM, Ehrlich J et al** – Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int* 2006; 69:1093
19. **Hillege HL, Nitsch D, Pfeffer MA et al** – Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; 113:671-678
20. **Harnett JD, Foley RN, Kent GM et al** – Congestive heart failure in hemodialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int* 1995; 47:884-890
21. **Levin A, Singer J, Thompson CR et al** – Prevalent left ventricular hypertrophy in the predialysis population: Identifying opportunities for intervention. *Am J Kidney Dis* 1996; 27:347-354
22. **Parfrey PS, Foley RN, Harnett JD et al** – Outcome and risk factors for left ventricular disorders in chronic uremia. *Nephrol Dial Transplant* 1996; 11:1277-1285
23. **London GM, Pannier B, Guerin AP et al** – Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: Follow-up of an Interventional Study, *J Am Soc Nephrol* 2001; 12: 2759-2767
24. **London GM** – Left ventricular hypertrophy: why does it happen? *Nephrol Dial Transplant*. 18(Suppl 8):viii2-viii6
25. **McClellan WM, Flanders WD, Langston R et al** – Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. *J Am Soc Nephrol* 2002; 13:1928-1936
26. **Al-Ahmad A, Rand WM, Manjunath G et al** – Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol,* 2001; 38:955-962
27. **Besarab A, Bolton WK, Browne JK et al** – The Effects of Normal as Compared with Low Hematocrit Values in Patients with Cardiac Disease Who Are Receiving Hemodialysis and Epoetin. *N Engl J Med* 1998; 339:584-590
28. **Foley RN, Parfrey PS, Morgan J et al** – Effect of haemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 2000; 58:1325-1335
29. **Parfrey P, Foley RN, Wittreich B et al** – Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 2005; 16:2180-2189
30. **Roger SD, McMahon LP, Clarkson A et al** – Effects of early and late intervention with epoetin on left ventricular mass among patients with chronic kidney disease (Stage 3 or 4): Results of a randomized clinical trial. *J Am Soc Nephrol* 2004; 15:148-156
31. **Cice G, Ferrara L, D'Andrea A et al** – Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003; 41:1438-1444
32. **Kalantar-Zadeh K, Block G, Humphreys MH et al** – Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003; 63:793-808
33. **Zager PG, Nikolic J, Brown RH et al** – "U" curve association of blood pressure and mortality in hemodialysis patients. *Kidney Int* 1998; 54:561-569
34. **Kalantar-Zadeh K, Kilpatrick RD, Kuwae N et al** – Reverse epidemiology: a spurious hypothesis

or a hardcore reality? *Blood Purif* 2005; 23:57-63

35. **Liu Y, Coresh J, Eustace JA et al** – Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2004; 291:451-459
36. **Suliman M, Stenvinkel P, Qureshi AR et al** – The reverse epidemiology of plasma total homocysteine as a mortality risk factor is related to the impact of wasting and inflammation. *Nephrol Dial Transplant* 2006; Sep 17
37. **Boaz M, Smetana S, Weinstein T et al** – Secondary prevention with antioxidants of cardiovascular disease in end-stage renal disease (SPACE): randomised placebo-controlled trial. *Lancet* 2000; 356:1213-1238
38. **Tepel M, van der Giet M, Statz M et al** – The Antioxidant Acetylcysteine Reduces Cardiovascular Events in Patients With End-Stage Renal Failure: A Randomized, Controlled Trial. *Circulation* 2003; 107:992-995
39. **Yilmaz MI, Saglam M, Caglar K et al** – The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine. *Am J Kidney Dis* 2006; 47:42-50
40. **Scholze A, Rinder C, Beige J et al** – Acetylcysteine reduces plasma homocysteine concentration and improves pulse pressure and endothelial function in patients with end-stage renal failure. *Circulation* 2004; 109:294-295.
41. **Locatelli F, Pisoni RL, Combe C et al** – Anaemia in hemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004; 19:2928
42. **Young EW, Akiba T, Albert JM et al** – Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) *Am J Kidney Dis* 2004; 44(Suppl 2):S34-S38
43. **Gaede P, Vedel P, Larsen N et al** – Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383-393
44. **Hampl H, Hennig L, Rosenberger C et al** – Effects of optimized heart failure therapy and anemia correction with epoetin beta on left ventricular mass in hemodialysis patients. *Am J Nephrol* 2005; 25:211-220