The Challenge of the Unacceptable High Mortality in End-Stage Kidney Disease: Is Folic Acid the Answer?

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In an article published in this issue of *Blood Purification*, Righetti et al. give evidence for a beneficial effect of low-dose folic acid treatment on cardiovascular morbidity compared to no supplement [1]. Two previous studies in hemodialysis patients have not shown a beneficial effect in groups comparing multivitamins and 1, 5 and 15 mg folic acid [2] or three different high-dose regimes of folic acid: 15, 30 and 60 mg [3]. Also in patients with chronic kidney disease, studied in the AFSAT trial (15 mg folic acid compared to placebo), no slowing of atheroma progression or a change in cardiovascular mortality and morbidity could be found [4]. In the general population the effect of homocysteine lowering by folic acid does not result in a lowering of the combined end point of vascular events and mortality, although there seems to be a trend towards less stroke incidence [5]. So there are different studies in different populations with different dose regimens and different results. What conclusions can be drawn from these interventions?

In all studies a significant lowering of total homocysteine has been observed. Although folic acid reduces the risk factor 'high plasma homocysteine', it is only part of the story. As discussed by the authors and also summarized by Suliman et al. [6], there is the paradoxical relationship in end-stage renal disease between high homocysteine and better survival. This may be explained by the fact that both malnutrition and diabetes lower homocys-

teine. So it may be that in some particular patient population a reduction in homocysteine may help and in others it may not. It may be that not lowering homocysteine but normalizing folic acid levels may explain the beneficial effect observed in some studies.

Is it necessary to repeat interventional trials that have proved unsuccessful in a general patient population? It has previously been claimed that findings in other populations can be transposed to patients with end-stage renal disease. Is this the case? Non-modifiable risk factors, e.g. age, previous cardiovascular problems and diabetes, are related to morbidity and mortality in the same way as in a general population. Amongst the modifiable risk factors, the relationship is less clear. Body weight, serum cholesterol, homocysteine and blood pressure are not or are even inversely correlated [7, 8]. These observations indicate that the impact of risk factors in the dialysis population is different and that observations in general cannot be transposed to dialysis patients. A lot of observational information has been collected. However we should only rely on prospective information to guide treatment.

What is the evidence from the few prospective randomized interventional trials that have been conducted in dialysis patients? Fosinopril has been studied in dialysis patients with left ventricular hypertrophy and, although the results have not been formally published, preliminary presentation revealed no significant effect on a combined

end point of mortality and cardiovascular morbidity [9, 10]. Similarly atorvastatin 20 mg did not show a beneficial effect on cardiovascular death and morbidity in type-2 diabetes patients on hemodialysis for a period of less than 2 years [11].

In dialysis patients with dilated cardiomyopathy, administration of carvedilol showed a reduction in cardiac deaths and hospitalization rate. In this relatively small study the reduction rate for all-cause mortality was 0.51 and for cardiovascular death 0.31 [12]. Patients with kidney disease, especially on renal replacement therapy, have increased oxidative stress. Two studies have shown that administration of acetylcysteine or vitamin E supplements decreases the risk of reaching a combined end point (death and cardiovascular event) [13, 14]. This is at variance with large studies in the general population showing that antioxidant treatment does not influence outcome. The three trials with folic acid and vitamin supplements show contradictory results. The reason for the discrepancy between the general and dialysis population remains obscure, but the point is that dialysis patients need to be considered as a particular and specific group. Moreover

the dialysis population is heterogeneous: hypertension, diabetes, kidney disease, gender and many other characteristics or co-morbidities may influence mortality and the effect of treatment. This is also illustrated in this study since nutrition influences outcome, especially in the treated group with low homocysteine.

Because mortality ranges between 15 and 30%/year, the 1-year post-myocardial infarction mortality is 59%, and because of the above-mentioned discrepancies between epidemiology and cardiovascular risk factors and the different results of controlled trials, there is an urgent need for new prospective trials to study the effects of both old and new drugs. These studies should be carefully designed, taking into account all available information in order to select patients correctly and to maximize the results of our work. The ultimate goal should be the reduction of mortality and morbidity in the dialysis population.

Nephrologists need to stimulate governments, scientific organizations, industry and everyone involved to overcome this unacceptable handicap of our patients.

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