Cardiovascular risk in uraemic patients—is it fully explained by classical risk factors?

Carmine Zoccali
CNR Centre of Clinical Physiology, Reggio C, Italy

What is a risk factor?
The definition of risk factor does not imply a causal association between the factor and the disease. A non-causal association between a risk factor and a disease may result when the factor in question is a marker for another causal factor (confounding) or when it reflects the disease itself (reverse causality). Many risk factors in dialysis patients are not causal, but reflect the severity of the uraemic syndrome. In itself, urea cannot be considered responsible for the high mortality seen in the dialysis population. However, the plasma concentration of this substance reflects the severity of the uraemic syndrome (disease marker), thus establishing a link between chronic uraemia and mortality. Non-
causal risk factors are useful to stratify patients and identify high-risk groups, but the identification of causal factors is essential for planning interventions aimed at reducing total and cardiovascular mortality. The scientific strategy for the identification of causal factors is complex [1] and includes the strength and the temporal sequence of the relationship between the risk factor and the disease, the pathophysiological plausibility of the underlying working hypothesis, and the results of intervention studies of risk factor modification (if an intervention that reduces a risk factor, reduces also cardiovascular complications, it is likely that this factor is a causal one).

**The epidemic of cardiovascular disease in uraemic patients**

Patients on chronic dialysis have an exceedingly high risk for cardiovascular disease. Cardiovascular risk factors in dialysis patients are in part similar to those in the general population. Diabetes, hypertension, left ventricular hypertrophy (LVH) and cardiac insufficiency, the main risk factors that have a high explanatory power for cardiovascular morbidity and mortality in the general population, are more prevalent in patients on dialysis than in the non-uraemic population [2]. The over-representation of these classical risk factors in the dialysis population would suggest that the high rate of cardiovascular complications in uraemic patients derives mainly from their being a selected population with high baseline risk (the renal consequences of atherosclerosis have coronary and cerebrovascular counterparts). In contrast, uraemic patients face the additional risks caused by hyperparathyroidism, anaemia, chronic volume expansion, hyperhomocystinaemia and a microinflammatory state. The weight of these risk factors in comparison with classical risk factors is still undefined although many are convinced that such factors specifically related to the uraemic state play a major role.

**Do classical cardiovascular risk factors explain the high mortality of dialysis patients?**

The Framingham risk equation is a powerful predictor for ischaemic heart disease [3]. This equation is based on eight parameters: age, sex, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, LVH and the presence of diabetes. If we calculate the 10-year risk of the ‘average’ dialysis patient of the Newfoundland database [4] (51-year-old, male, blood pressure 151/83 mmHg, serum cholesterol 205 mg/dl, HDL cholesterol 40 mg/dl, with LVH, non-diabetic and smoker) the expected risk for coronary heart disease is 44%, which is much higher than the risk of the general population (10%). However, the truly striking observation to be made is that the actual risk observed in Newfoundland dialysis patients was even higher than the predicted risk because only about the 10% of dialysis patients of the inception cohort survived for longer than 6 years [4], cardiovascular mortality representing 59% of the overall mortality. This observation is an indication that, in uraemic patients, peculiar risk factors are operative in addition to those which they share with the general population. In a similar vein, Coronado et al. [5] calculated that the predicted risk (extrapolated to zero (glomerular filtration rate (GFR)) for cardiovascular complications in the MDRD cohort was much lower than the actual risk in the North American dialysis population.

**Classical cardiovascular risk factors in uraemic patients**

**Hypertension**

Hypertension is much more prevalent in dialysis patients than in the general population. About 50–90% of dialysis patients are hypertensive (blood pressure >140/90 mmHg), whereas the frequency of hypertension in age- and sex-matched control subjects does not exceed 25%. In the general population an extensive meta-analysis by McMahon and co-workers showed that the risk of cardiovascular events is linearly related to diastolic pressure, and that such a relationship holds true even in the range of normotensive blood pressure values. Interestingly the risk reduction conferred by anti-hypertensive treatment is close to that predicted by this meta-analysis [6]. In contrast, analysis of large haemodialysis databases has shown that the risk of mortality is U-shaped being higher among patients who are markedly hypertensive or markedly hypotensive after dialysis, and lowest for those with a systolic blood pressure in the 150–159 mmHg range [7]. However, these findings in no way imply that hypertension in dialysis patients is a harmless condition. Indeed, a follow-up study has shown that a 10-mmHg blood pressure increase is associated with a 44% higher risk of developing congestive heart failure (CHF) and that patients with LVH or CHF are at a much higher risk of mortality than patients without these complications [8]. Heart failure lowers blood pressure and the prevalence of heart failure is very high (>40%) in both incident and prevalent haemodialysis patients. Thus low blood pressure is a marker of severe cardiac disease rather than a causal risk factor for cardiovascular mortality in the dialysis population (reverse causality).

**Cholesterol and lipoprotein (a)**

The prevalence of hypercholesterolaemia in dialysis patients does not exceed that in the general population. This finding reflects the high frequency of malnutrition in chronic renal failure. The relationship between serum cholesterol and total mortality in the dialysis population offers an even more obvious example of reverse causality. The risk of death is 4.3 times higher in haemodialysis patients with serum cholesterol <100 mg/dl than in those with values between 200
and 250 mg/dl [9]. Again, such a relationship does not imply that high cholesterol is innocuous, but reflects the fact low cholesterol is a marker of terminal disease.

Lipoprotein (a) (Lp(a)) results from an apolipoprotein (a) (apo(a)) linked to a low-density lipoprotein (LDL) particle. Lp(a) levels are raised markedly in dialysis patients and cross-sectional data show that the presence of coronary heart disease is associated with smaller apo(a) phenotypes, lower high-density lipoprotein (HDL), higher apo B and fibrinogen in prevalent haemodialysis patients [10]. Presently there is no evidence that selective pharmacological intervention to lower Lp(a) reduces the risk of cardiovascular disease.

Other risk factors and factors peculiar to chronic renal failure

Besides the classical risk factors discussed previously, anaemia, hyperhomocysteinaemia, hyperphosphataemia and hyperparathyroidism and a chronic microinflammatory state presumably amplify the cardiovascular risk in the dialysis population.

Anaemia

Anaemia has a negative impact not only on quality, but also on quantity of life. In patients with severe anaemia (haematocrit < 27%) mortality is higher by 60% compared with patients with moderate anaemia (31–33%) [11]. This is important because anaemia is a modifiable risk factor. The recent Normal Haematocrit Trial [12] in patients with cardiac disease compared the effects of rhEpo treatment aiming at a normal haematocrit (42%) versus a conventional target (30%). This study showed that survival in the normal haematocrit group was less than in the control group. Although the interpretation of this study is debated [13], by now the wise nephrologist should not aim at raising the haematocrit beyond the currently recommended target (33–36%) in dialysis patients with cardiac disease. Whether a normal haematocrit affords cardiovascular protection in patients without cardiac disease remains to be established.

Homocysteine

Homocysteine is a sulphur amino acid, the metabolism of which depends on vitamin B12 and folic acid. The plasma levels of homocysteine are raised markedly in dialysis patients. In a recent cohort study high homocysteine was associated with high cardiovascular morbidity and mortality [14]. However, it remains uncertain whether this association is truly independent of other cardiovascular risk factors, such as malnutrition and inflammation. High-dose folate (5–15 mg/day) reduces the serum concentration of homocysteine, but there are no prospective studies showing that lowering serum homocysteine reduces cardiovascular morbidity and mortality. The need to perform an intervention study aimed at assessing the effect of high dose folate on cardiovascular complications in dialysis patients has recently been emphasized, not least because of pharmacoeconomic considerations [15].

Hyperparathyroidism–hyperphosphataemia

Many clinical and experimental studies show that hyperparathyroidism and hyperphosphataemia are related to cardiovascular damage in dialysis patients. However, looking at the phenomenon from an epidemiological perspective the picture is rather complex because serum parathyroid hormone per se fails to significantly predict an increased risk of death. In contrast hyperphosphataemia is definitely associated with higher mortality [16]. This finding is of importance because hyperphosphataemia is a modifiable risk factor.

Chronic inflammatory processes

In recent years C reactive protein (CRP) has emerged as a strong predictor for cardiovascular complications in dialysis patients. Two years survival is 90% in those with normal CRP and less than 60% in those with raised values [17]. CRP per se is unlikely to be a causal factor, but it is a very strong indicator of enhanced cardiovascular risk and is tightly correlated with the severity of atherosclerosis [18]. Serum IgG anti-Chlamydia pneumoniae titres are correlated with CRP suggesting that chlamydial infections may contribute to the elevation of CRP in these patients [18]. Although bacterial contamination of the dialysis fluid is suspected to be an important cause of the raised CRP of dialysis patients, available evidence suggests that the dialysis procedure is unlikely to be the sole (or the most important) factor of raised CRP. The identification of these factors is of obvious importance if we are to devise new strategies aimed at reducing cardiovascular complications in the dialysis population.

References

8. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. Impact of hypertension on cardiomyopathy, morbidity...