# Summary

The rising tide of chronic renal failure (CRF) has resulted in an increasing number of patients starting dialysis, placing an ever greater burden not only on the nephrology community, but also on the whole society.

Patients receiving maintenance dialysis have a mortality rate surpassing that of many cancers, with a large proportion of these deaths occurring from cardiovascular causes. Treating cardiovascular disease in dialysis patients has thus become the main focus for everyday nephrology practice. It took decades since the initial conception of the Framingham study to develop paradigms for treatment of cardiovascular disease in the general population. It may seem plausible to apply the same paradigms to patients with CKD, as long as there is reasonable proof to indicate that their response to such measures is similar to what we expect from other patients. Such proof would start by showing an association in observational studies between the risk factor(s) in question and an outcome, such as mortality, followed by clinical trials indicating improved outcomes following modifications of these risk factors.

The paucity of clinical trials in the field of nephrology has mostly left us with observational studies when trying to determine what our best clinical practices should be. It has been very confusing that a significant body of observational research indicated an association between the ‘‘classical’’ cardiovascular risk factors (such as obesity, hypertension and high cholesterol) and mortality in dialysis patients is opposite to what we see in the general population. This phenomenon was called ‘‘reverse epidemiology’’ or ‘‘risk factor paradox,’’ resulted in an ongoing debate

about the plausibility of the associations and the applicability of these findings in everyday practice.

Atherosclerotic cardiovascular disease **(ACD)** is a major cause of mortality in patients undergoing dialysis therapy. Despite significant progress in dialysis technology, the prevalence of ACD has not decreased

Also Epidemiological studies repeatedly and consistently showed that a strong association between clinical outcome and measures of both malnutrition and inflammation in dialysis patients.

By reconciling relation between malnutrition, inflammation and cardiovascular disease it was found that:

- Malnutrition in ESRD patients are largely the consquence of heart disease (e.g. cardiac failure ) or are caused by factors (infection, inflammation) that at the same time trigger the development of atherosclerotic cardiovascular disease
- Proinflammaory cytokines generated in response to cardiac failure, infection and inflammation may cause muscle wasting, hypoalbuminemia, and anorexia as well as reduced cardiac contractility and vascular disease
- A synergism between different mechanisms in developing atherosclerosis in uremia

The phenomenon of risk factor paradox is caused or at least accentuated by MICS in several ways:

First, patients who are underweight or have low serum cholesterol, creatinine, or homocysteine levels may have MICS and its poor outcome. Thus, MICS may both cause these alterations and be associated with

increased mortality, caused by either the illnesses that engender MICS or the atherosclerotic cardiovascular diseases that seem to be promoted by MICS.

Second, these paradoxical factors may indicate a state of undernutrition, which may predispose to infection or other inflammatory processes.

Finally, it has been argued that when individuals are malnourished, they are more susceptible to the ravages of inflammatory diseases. Hence, a condition that potentially attenuates the magnitude of PEM or inflammation should be favorable to dialysis patients.

Elements of reverse epidemiology are:

- Body mass index.
- Total cholesterol level.
- Low density lipoproteins.
- Hypertension either systolic or diastolic.
- Serum homocysteine.
- Serum creatinine level.
- Serum parathyroid hormone.

This phenomenon of reverse epidemiology makes it sometimes difficult to target traditional risk factors in an effective manner because determination of an optimal target for risk factors such as blood pressure and LDL-cholesterol has become uncertain, especially in patients with advanced stages of CKD.

Studies of an interventional nature, including randomized prospective clinical trials, will probably be necessary to achieve these goals. This dilemma reflects both the strengths and the limitations of epidemiological studies. These studies are excellent for hypothesis generation, but they generally cannot prove causal relationships.