Cardiovascular risk in patients with renal disease: treating the risk or treating the risk factor?

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Keywords: antiplatelet therapy; blood pressure control; cardiovascular risk; folic acid; lipid-lowering treatment

Introduction

Cardiovascular mortality in patients with end-stage renal failure is probably among the highest in medicine. In the younger age group (25–34 years) this may exceed the cardiovascular mortality risk of a normal population by several hundred times, while in the age segment 45–55 years it is still more than 50 times the normal annual mortality [1,2]. From this observation, two important lessons are to be learned.

(i) Normally the atherosclerosis process takes decades to develop to a clinically relevant extent. The fact that these young subjects already have such a high cardiovascular mortality indicates that in the phase before arriving at end-stage renal failure, most of the cardiovascular damage has already occurred. Indeed, several studies and surveys have demonstrated that even mild renal impairment already carries an increased risk for cardiovascular death [3,4]. Therefore, any strategy to reduce this very high cardiovascular mortality should start early in the process.

(ii) The absolute risk that patients with renal disease die from cardiovascular complications is extremely high. In fact, the absolute risk exceeds that of patients that already had a previous myocardial infarction. This is important to realize. As was recently discussed by Law and Wald [5], reducing the value of a risk factor, such as cholesterol or blood pressure, is associated with a proportional reduction of cardiovascular risk, irrespective of the starting level of the risk factor. Thus, lowering cholesterol from 9 to 8 mmol/l is associated with an ~20% risk reduction, but so is cholesterol lowering from 5 to 4 mmol/l. Likewise, blood pressure reduction reduces cardiovascular risk not only going from diastolic blood pressures of 110 to 100 mmHg, but also from 85 to 75 mmHg. Although one could theorize that at very low levels of a risk factor the beneficial effect of risk factor reduction may be lost (known as a U-curve), it is important to realize that down to the lower limits of normal values this relationship is maintained [5].

Importance of absolute risk

Obviously, the indication for treatment of such a risk factor is determined by the absolute risk that the patient will die from cardiovascular disease. Normally, in the low cholesterol range or the low blood pressure range the absolute risk is not so high, so therefore these patients would not be treated. On the other hand, in the high cholesterol and high blood pressure range the absolute risk of these patients is relatively high and benefits of such treatment can be found. This story is different if one looks at patients who have a priori a very high cardiovascular risk, such as patients with end-stage renal disease. Here, modulation of risk factors even in what we could consider ‘normal’ values may have large effects on absolute cardiovascular mortality. Indeed, recent studies in patients with high cardiovascular risk, such as patients that already had a myocardial infarction, have shown that lipid lowering with statins has similar reductions in cardiovascular mortality whether one lowers cholesterol from normal values to very low values or from high values to normal values [6]. Based on this concept it should be considered that all reversible cardiovascular risk factors that can be modified should be modified in patients with end-stage renal disease.

Lipid-lowering treatment for all patients with end-stage renal disease?

This would mean that all patients with renal disease should be treated with a statin, irrespective of their cholesterol level (at least down to the lower limit of the normal range). There are no reasons to assume that patients with renal disease would be an exception.
where lipid lowering would not have a beneficial effect on cardiovascular mortality. If that is true then lowering cholesterol from relatively normal levels to lower levels would still carry an ~20% risk reduction, which on the background of the very high absolute mortality in these patients would be extremely beneficial. Recently, an international study has started that exactly addresses this issue. In the AURORA study, in a double-blind randomized set-up, addition of rosuvastatin on top of regular therapy is compared with placebo in prevention of cardiovascular events. Patients with renal disease may also have specific lipid abnormalities. These appear mostly to be related to increased very low-density lipoprotein secretion secondary to high free fatty acid fluxes [7]. In this respect, drugs that reduce such free fatty acid fluxes (e.g. thiazolidinedione derivates) could appear useful in the future for such patients.

**Importance of optimal blood pressure control**

Down to at least a blood pressure of 118/76 mmHg, cardiovascular risk reduction is maintained [8,9]. Therefore, any blood pressure reduction to such low values would carry a further reduction in cardiovascular mortality. In fact, this principle has been recognized in several studies where the effect of blood pressure lowering on progression of renal disease was studied. Also, in these studies such low blood pressure values still led to further organ preservation [10]. In this respect it is important to realize that increased sympathetic tone in patients with end-stage renal disease plays an important role in the maintenance of the high blood pressure and as well as the cardiovascular risk [11]. Like in the studies looking at progression of renal disease as an endpoint, angiotensin-converting enzyme inhibitors or AT1 receptor blockers may be more advantageous than other antihypertensive drugs, as these drugs restore increased sympathetic tone as well as indices of cardiovascular disease, such as vessel wall stiffness [9,11,12].

**How about antiplatelet therapy?**

In conditions that are associated with a high absolute cardiovascular risk, aspirin therapy has led to reductions in cardiovascular mortality [13]. This remains a controversial issue in patients with end-stage renal disease, because the paradigm is that these patients have uraemic trombopathy. However, it should be noted that platelet vessel wall interaction is mainly controlled by three agents [14]. One is exposure and expression of matrix proteins and adhesion proteins, such as collagen and von Willebrand factor, which are increased in patients with end-stage renal disease. These adhesive molecules react with platelet proteins, such as glycoprotein IIbIIIa. Here, there is a mild defect in patients with end-stage renal disease. However, the main reason why patients with end-stage renal disease used to have uraemic trombopathy is the fact that they used to be anaemic, as platelet transport to the vessel wall requires erythrocytes. Nowadays, with erythropoietin therapy, this defect is hardly present anymore, while at the same time these patients usually have high fibrinogen levels and can be considered as patients with hypercoagulability. Therefore, if there are no contraindications and bleeding is present, aspirin therapy can be recommended.

**Usefulness of systematic folate supplementation**

Patients with renal disease can be considered as patients that are relatively folate deficient [15]. This is due to a combination of factors where restricted intake, impaired absorption due to reduction of folate conjugase, reduced utilization and losses with haemo and peritoneal dialyses play a role at the same time. Folic acid is crucial for re-methylation of homocysteine and thus prevention of hyperhomocysteaemia, but it also has direct effects on atherosclerosis defence by increasing the activity of the endothelial nitric oxide system [16]. Since there are no obvious side effects, it is probably a good idea to give all patients with end-stage renal disease at least 1 mg folic acid per day. Indeed, studies in children with end-stage renal failure have shown that high-dose folate therapy (5 mg/m\(^2\)) improved endothelial function as an indicator of defence against atherosclerosis [17].

Finally, one may consider giving these patients antioxidants. However, this is still a controversial subject, as in other groups with high cardiovascular risk, placebo-controlled trials could not show a beneficial effect [18,19]. Nevertheless, there are some small-scale studies showing a beneficial effect of antioxidant therapy in dialysis populations [20,21].

**Other disease-specific risk factors**

Apart from these general risk factor modulations, which in view of the high absolute cardiovascular mortality in these patients may have large beneficial effects, patients with end-stage renal disease also have disease-specific factors that further contribute to their very high cardiovascular mortality. One interesting aspect is that hearts and kidneys of patients with end-stage renal disease show a strikingly reduced capillary density [22]. Recent data have shown that bone marrow-derived progenitor cells, which coordinate and facilitate processes such as capillary repair and angiogenesis, are reduced in patients with end-stage renal disease, while such progenitor cells can be mobilized by erythropoietin [23]. Therefore, relative erythropoietin deficiency and/or a stem cell defect may have contributed to the loss of capillaries and resulted in fibrosis and hypoxia at tissue levels.
The second important phenomenon is that deranged calcium–phosphate metabolism probably contributes to calcification of the vasculature. Indeed, a very prominent feature of cardiovascular disease in patients with end-stage renal disease is the extensive calcification of the vascular tree [24]. The introduction of new drugs to control hyperphosphataemia, such as sevelamer, instead of calcium-containing products and the introduction of calcimimetics in the near future might help to better control the secondary hyperparathyroidism and associated vascular calcification in renal patients.

**Drug prescription vs lifestyle changes**

If one surveys all these recommendations to control cardiovascular mortality in patients with end-stage renal disease, the renal physician is confronted with a formidable task. In general, patients with end-stage renal disease have on average 10–11 different drugs and following the recommendations as described above would increase that number even further [25]. On top of that, these patients should also be intensively guided in lifestyle management, such as stimulation of exercise and cessation of smoking. At the same time, the developments in hospitals are more to focus on cure and not so much on prevention, to focus on short stay and day care rather than on prolonged patient contacts. If we are really serious with prevention of cardiovascular disease, we probably should radically redesign our care process. A proposal, therefore, is to use the nephrologist as a director of the care process. He/she is the person to set the guidelines and to tailor these guidelines for a specific patient.

Nurse practitioners or other advanced nursing staff can then be used as case managers to stimulate patients to adhere to lifestyle advice and adherence to drug therapy. Obviously, such care does not necessarily need to be within the hospital environment. It is crucial, however, that insurance companies recognize the importance of cardiovascular prevention strategies in renal patients and reimburse such initiatives. Modern informatics developments, such as an electronic patient file, can facilitate such a redesign of the care process as guidelines and individual recommendations can be incorporated and hardwired in diagnostic work-up and control visits. I believe that this is truly a very important mission in modern nephrology. Renal replacement therapy is a symptomatic therapy that does not reduce cardiovascular mortality or improve quality of life. In this respect I would like to quote Franz Volhard who wrote in 1918, ‘Treatment of patients with renal disease should start with doctors forgetting about nephritis. In the case of patients with renal disease it is basically a premature aging process of the vessels and the patient should be approached as a human being who wants to become old’ [26].

Conflict of interest statement. None declared.

**References**

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Flowing time on the peritoneal membrane

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**Keywords:** ageing; biocompatibility; peritoneal dialysis; ultrafiltration

Time, passing on, rhythms our lives. This observation also applies to physiology and pathophysiology. It is known that this seasonal adaptability is based both on genetic programmes, and on a strict neurovegetative and endocrinological control, with a flexible and sophisticated network of activities changing in relation to external stimuli and aging, starting in intrauterine life to the years of growth, adulthood and senility. Likewise, the peritoneum of peritoneal dialysis (PD) patients responds to the passing of time by undergoing anatomical and functional changes (Figure 1).

Although the functional characteristics of the peritoneum in children undergoing PD are different from those in adult patients, recent experimental studies have demonstrated that, when adjusted in relation to body surface and age, there are no significant differences in peritoneal fluids and solutes transport between adults and children. In a recent study on children under PD, time was found to have no effect on parameters for peritoneal transport, except for the restriction coefficient for macromolecules [1].

Factors involved in peritoneal ultrafiltration failure

A large body of data demonstrates that the risk of encountering a clinically relevant reduction in peritoneal ultrafiltration increases in relation to the time of PD, and this risk is estimated to be ~35% after 6 years of treatment [2]. Ambulatory PD (APD) or continuous ambulatory PD (CAPD) modalities do not have a significant influence on small solute transport or fluid kinetics [3]. Currently, four mechanisms are known to underlie failure in peritoneal ultrafiltration [4]. Different data demonstrate that aquaporin-mediated water transport is altered in patients under long-standing PD [5,6]. An increased peritoneal absorption of small osmotically active solutes, followed by a dramatic fall in the osmotic gradient, is a common and widely known mechanism in decreasing ultrafiltration [7]. A hypopermeable peritoneum with loss of peritoneal surface area, typically after severe peritonitis with adhesions, or in the case of sclerosing peritonitis, is probably a rare mechanism of effective ultrafiltration failure. A poor effective ultrafiltration due to high lymphatic absorption rates is also considered of particular importance in peritoneal aging [8].

Structural and functional changes of peritoneal wall

Various morphologic and structural alterations can occur in the peritoneal tissue, especially after long-standing PD. The most frequently described alteration in the peritoneum of patients on long-standing PD is the formation of a layer of collagenous, acellular material replacing the mesothelial surface. The peritoneum of patients with this type of alteration contains groups of cells exposed to degenerative phenomena, including intracellular oedema, destruction and degene-