Benefits from angiotensin-converting enzyme inhibition in patients with renal failure: latest results


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Introduction

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic renal failure and end-stage renal disease (ESRD). The high risk for CVD results from the additive effect of multiple factors, including haemodynamic overload and several metabolic and endocrine abnormalities that are more or less specific to uraemia or its treatment modalities. CVD includes disorders of cardiac structure and function (left ventricular hypertrophy [LVH], cardiomyopathy), and disorders of the vascular system (atherosclerosis, arteriosclerosis). These two groups of disorders are frequently associated and can exacerbate each other.

Epidemiological and clinical studies have shown that cardiovascular disease is a major contributory factor to high morbidity and mortality in patients with end-stage renal disease (ESRD). This excess mortality is related principally to left ventricular hypertrophy (LVH) and increased arterial stiffness and their interaction. Recent findings have indicated that aortic pulse wave velocity (PWV), a marker of aortic stiffness, is a strong independent predictor of cardiovascular and all-cause mortality in patients with ESRD who are on haemodialysis. Furthermore, it was shown in a therapeutic trial that the lack of aortic PWV attenuation despite significant drug-induced reduction in blood pressure was a significant predictor of cardiovascular death in patients with ESRD. Moreover, the absence of PWV attenuation was associated with lack of regression of LVH, which by itself was associated with poor outcome. Controlled trials have also shown that angiotensin-converting enzyme inhibitors are the most efficient drugs for regression of LVH. Moreover, independently of its effects on left ventricular mass and blood pressure, the prescription of the ACE inhibitor perindopril, whether in combination or alone, had a strong and independent beneficial impact on all-cause and cardiovascular survival. After adjustment for all confounding factors, the risk ratio for perindopril use was 0.19 for all-cause mortality and 0.18 for cardiovascular mortality. These results indicate that, in patients with ESRD, improvement in arterial stiffness and regression of LVH are associated with a better prognosis and that the use of the ACE inhibitor perindopril has a favourable effect on survival that is independent of haemodynamic alterations.

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Principal cardiovascular alterations in chronic renal disease

Cross-sectional studies have shown that LVH is the most frequent cardiac alteration in ESRD and is an ominous prognostic sign.²–⁵ The prevalence of left ventricular alterations, including LVH, is high among patients with chronic renal failure and ESRD in all age groups, including children.³ On starting dialysis 75% of adults have LVH, with concentric hypertrophy in 42% of patients and left ventricular enlargement (eccentric hypertrophy) in 44% of patients.⁴ The increase in left ventricular mass in patients with ESRD results from a mild enlargement of the left ventricular end-diastolic diameter and/or an increased left ventricular wall thickness, and combines the features of eccentric and concentric hypertrophy.⁴,⁶,⁷ The LVH in patients with ESRD is due principally to a chronic increase in stroke work and left ventricular minute work resulting from an association of combined volume and pressure overload.⁶,⁷

Volume/flow overload

The LVH is associated with increased stroke and cardiac index, and is most likely attributable to chronic volume/flow overload associated with three principal factors: sodium and water retention; arteriovenous (AV) shunts; and anaemia.⁶–¹³ Regression of LVH in patients on haemodialysis could be achieved by ultrafiltration and reduced salt intake.⁹,¹⁰ The presence of an AV shunt lowers peripheral resistance, and blood pressure is maintained through elevation of cardiac output, via increased heart rate and stroke volume.⁶,⁷ These changes induce increases in left ventricular diameter and mass, which are significantly associated with AV fistula flow.⁶ Long-term effects of high-flow AV shunts can adversely affect cardiac function. Cardiomegaly with high-output cardiac insufficiency occurs as a complication of high-flow AV shunts. The creation of an AV shunt for haemodialysis access is in part responsible for left ventricular dilatation and the high-output state.¹¹

Anaemia is associated with functional alterations with the ultimate goal of maintaining optimal oxygen delivery to tissues and organs. Maintenance of adequate organ oxygenation is achieved both by non-haemodynamic and haemodynamic adaptation. The most typical haemodynamic change observed is increased cardiac output due to high stroke volume and increased heart rate.¹² The prospective multicentre Canadian cohort study in early renal disease identified decline in haemoglobin level (and increase in systolic blood pressure) as the principal predictors of LVH and its progression.⁸ The odds ratio for progression of LVH is 1.32 for each 0.5 g/dl decrease in haemoglobin.⁸ Similar observations were made in patients with ESRD. After adjusting for age, diabetes, ischaemic heart disease, blood pressure and serum albumin levels, each 10 g/l decrease in haemoglobin level was independently associated with left ventricular dilatation (odds ratio 1.46).¹³ Several studies of chronic renal failure and ESRD have shown that partial or complete correction of anaemia with erythropoietin decreases the cardiac output and heart rate, and induces partial regression of LVH.¹⁴,¹⁵

Pressure overload

In a prospective study in ERD, Levin et al.⁸ showed that increased systolic blood pressure is an independent predictor of LVH and left ventricular growth (odds ratio 1.11 for each 5 mmHg increase). In patients with ESRD, LVH is closely related to systolic or pulse pressure.⁶,⁷,¹⁶ Pulse pressure is an independent cardiovascular risk factor in the general population, and recent epidemiological studies have shown that pulse pressure is associated with risk for death in patients undergoing haemodialysis.¹⁷,¹⁸ Systolic blood pressure as well as pulse pressure are simplified markers of pressure load, and result from the interaction between cardiac factors (stroke volume, ejection velocity) and the opposition to left ventricular ejection. The arterial factor(s) that oppose left ventricular ejection are peripheral resistance, stiffness of the aorta and large central arteries, and intensity and timing of wave reflections.¹⁹ (The fourth factor that opposes ventricular ejection is the inertial forces due to the mass of blood in the aorta and left ventricle.) With progression of anaemia and decrease in blood viscosity and the creation of AV shunts, the peripheral resistance is most frequently normal or lower in uncomplicated ESRD, and the principal ‘pressure’ factors that oppose ventricular ejection are arterial stiffness and early return of wave reflections.¹⁶,²⁰,²¹ Arterial stiffness is the principal determinant of systolic and pulse pressures in patients with ESRD and is closely associated with LVH²⁰,²¹ and its progression over time.²² Recent prospective studies have demonstrated that aortic stiffness and early wave reflections are independent predictors of all-cause and cardiovascular mortality in patients with ESRD²³,²⁴ and in the
LVH and arterial stiffness in risk reduction strategies in ESRD

LVH and arterial stiffness are the two principal cardiovascular complications associated with poor outcome. Several studies were undertaken to analyze the best strategies for reduction of the risk associated with these two complications. Because LVH is due to a combined volume and pressure overload, the principal therapeutic strategies were aimed at simultaneous reduction of these two complications. It was shown that regression of left ventricular mass was more related to the drug used than to the antihypertensive effect as such. Following treatment of patients with ESRD for 12 months with the calcium channel blocker nitrendipine and the angiotensin-converting enzyme (ACE) inhibitor perindopril, it was shown that for the same reduction in blood pressure, wave reflections and pulse wave velocity (PWV), only the group treated with perindopril exhibited a significant regression in LVH. In that study, the primary end-point was regression of left ventricular mass. Nevertheless, because arterial stiffness and LVH are associated with death, several other prospective studies were undertaken to analyze the survival of patients who underwent therapeutic intervention.

Arterial stiffness is partly dependent on operating blood pressure, and a decrease in blood pressure would ‘normally’ decrease stiffness. A recent trial demonstrated that reduction in aortic PWV in parallel to a reduction in blood pressure was associated with improved survival. The objective of the trial was to reduce cardiovascular morbidity and mortality through a therapeutic regimen successively involving salt and water depletion by dialysis; then, after randomization, ACE inhibition with perindopril or calcium channel blockade with nitrendipine; and finally the combination of the two agents and/or their combination with a beta-blocker. Using this procedure, it was possible to evaluate over long-term follow-up (51 months) whether the drug-induced mean blood pressure reduction was associated with a parallel decrease in arterial stiffness with resulting consequences for cardiovascular risk. During the follow-up, it was clearly shown that mean blood pressure, pulse pressure and aortic PWV were reduced in parallel in survivors. In contrast, in those who died from cardiovascular events, mean blood pressure was lowered to the same extent as in survivors, but neither pulse pressure nor PWV were significantly modified by drug treatment.

The results of that study indicated that survival of patients with ESRD was significantly better for patients whose aortic PWV declined in response to blood pressure lowering. The adjusted relative risks for all-cause and cardiovascular mortality in those patients whose PWV did not decline in response to blood pressure changes were 2.59 (95% confidence interval [CI] 1.51—4.43) and 2.35 (95% CI 1.23—4.51), respectively (P < 0.01). The prognostic value of PWV sensitivity to blood pressure lowering on survival was independent of age, blood pressure changes including pulse pressure, and blood-chemistry abnormalities.

The findings reported by Guérin et al. indicate that arterial stiffness is not only a risk factor contributing to the development of cardiovascular disease but also a marker of established more advanced, less reversible arterial changes. This concept is supported by the loss of aortic PWV sensitivity to blood pressure lowering in non-survivors in comparison with survivors, in whom arterial stiffness remained pressure sensitive. Furthermore, in that trial, prolonged survival appeared to reflect more closely the use of perindopril than the other drugs or the number of drugs per se. Indeed, the same study also demonstrated that the use of perindopril had a favourable and blood pressure- and PWV-independent effect on survival. In the Cox model, the risk ratio for perindopril use was 0.19 (95% CI 0.14—0.43) for all-cause mortality and 0.18 (95% CI 0.05—0.55) for cardiovascular mortality. The raw association (Kaplan–Meier) of perindopril prescription and mortality is shown in Fig. 1. There was no direct relationship between use of beta-blockers and/or dihydropyridine calcium channel blockers and outcome.

From another therapeutic trial in patients with ESRD, the same group demonstrated that partial regression of LVH was obtained by parallel treatment of anaemia and pressure overload. The partial regression of LVH had a favourable effect on both cardiovascular and all-cause survival. Nevertheless, regression of left ventricular mass was closely related to the therapeutic response of aortic PWV, and LVH regressed only in those patients in whom PWV decreased in response to therapeutic intervention.

Taken together, the results of these therapeutic interventions in patients with ESRD show that partial regression of LVH associated with sensitivity of arterial stiffness to decreased blood
pressure had a positive impact on all-cause and cardiovascular mortality. Furthermore, these studies indicate that ACE inhibition with perindopril had an additive, independent effect on regression of LVH and survival.

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References
