Prevalence of cardiovascular damage in early renal disease

Adeera Levin

University of British Columbia, Renal Insufficiency Clinic, Vancouver, Canada

Abstract
There is a large burden of cardiovascular disease in early renal disease due to multiple risk factors. Although left ventricular hypertrophy (LVH) is prevalent early in the process of progressive renal decline, it is associated with a number of modifiable risk factors (e.g. anaemia and systolic blood pressure (BP)). More importantly, treatment of modifiable risk factors in renal disease can delay progression. It is important to define anaemia physiologically and to remember that it is also associated with a number of cardiovascular risk factors that may or may not be independent of each other. In a recent prospective, multicentre Canadian study of early renal disease patients prior to dialysis (n = 446), the baseline prevalence of LVH increased both with decreasing renal function and decreasing haemoglobin (Hb) levels. Notably, Hb levels within current guideline target levels were still associated with a very high degree of LVH. Over a 12-month period, only a decrease in Hb and an increase in systolic BP, and baseline left ventricular mass index (LVMl) predicted left ventricular growth. Patients whose cardiac symptoms progressed over 12 months were those who experienced a significant fall in BP and a significant increase in LVMl during that time. In the future, steps are needed to ensure early identification of both renal disease and specific risk factors. Recognizing modifiable risk factors and addressing them early in the course of renal disease will facilitate the improvement of patient outcomes.

Keywords: anaemia; cardiovascular disease; left ventricular hypertrophy; pre-dialysis; progressive renal insufficiency

Introduction
Cardiovascular disease (CVD) is prevalent in end-stage renal disease (ESRD). In patients starting dialysis, ~75% have left ventricular hypertrophy (LVH) and ~40% have angina, coronary artery disease or peripheral vascular disease [1,2]. Indeed, CVD accounts for a significant portion of morbidity and mortality in ESRD patients, accounting for nearly half of all deaths in patients receiving dialysis for chronic renal failure (CRF) [3]. In view of the time required for the development of such CVD, it probably exists in a substantial proportion of patients prior to dialysis.

It is well established that, in an individual patient, the burden of illness is related to the risk factors and the time that these factors are present. In patients with renal disease, multiple risk factors occur for a long period of time, and there may be amplifiers or lack of inhibitors that contribute to the impact of these risk factors. Therefore, a number of strategies need to be developed before initiation of dialysis in order to change patient outcomes after they have started dialysis.

Cardiovascular disease burden of early renal disease
The high prevalence of CVD in renal disease is due to a cumulative series of risk factors. These can be considered as non-modifiable (e.g. age, sex, family history, diabetes, etc.), modifiable (e.g. smoking, hypertension, dyslipidaemia, etc.), and uraemia-specific (e.g. anaemia, hyperparathyroidism, impaired glomerular filtration rate, etc.). Together these factors can result in CVD manifested as congestive heart failure (CHF), LVH, coronary artery disease, peripheral vascular disease, myocardial infarction, etc.

The burden of CVD in early renal disease is indicated by the findings of a recent Framingham Offspring community-based study [4]. In a cohort of 6233 subjects examined prospectively for 15 years, those with mild renal insufficiency (~8%; serum creatinine 120–265 μmol/l) had almost double the prevalence of CVD as those without renal disease. Subjects with mild renal insufficiency also had a higher prevalence of coronary artery disease, CHF, LVH and cardiac medication use (Figure 1). Therefore, mild
renal insufficiency is common in the community and is associated with a high prevalence of CVD.

Cardiovascular risk factors in prior to dialysis patients with renal insufficiency

The prevalence of LVH and CVD in early renal disease patients prior to dialysis was recently examined in a prospective, multicentre, longitudinal Canadian cohort study [5]. This study evaluated modifiable risk factors for LVH and left ventricular growth (LVG), prevalence of symptomatic heart disease, correlates of hospitalization and prevalence of anaemia in pre-dialysis patients with renal insufficiency.

The population \( (n=446) \) was predominantly Caucasian (86%) with a mean duration of renal disease of 6.6 years and mean creatinine clearance of 36.3 ml/min. No patient was receiving epoetin therapy or had an arteriovenous fistula. The population was representative of the ESRD population in both Canada and Europe with respect to the causes of renal disease (e.g. hypertension 25%, diabetes mellitus 23%, glomerulonephritis 18%). The primary study outcome was the change in left ventricular mass index (LVMI) over 12 months; secondary outcomes included cardiovascular symptoms (according to the New York Heart Association (NYHA) classification for CHF and the Canadian Cardiovascular Society (CCS) classification for angina), number of hospitalizations and renal function.

The baseline prevalence of LVH increased both with decreasing renal function and with decreasing haemoglobin (Hb) levels (Figure 2). Notably, Hb levels within the current target levels recommended by the European Best Practice Guidelines [6] for a dialysis population are still associated with a very high degree of LVH. Patients with LVH at baseline had significantly lower renal function, lower Hb and higher systolic blood pressure (BP) values than those without LVH (Table 1). The use of angiotensin-converting enzyme (ACE) inhibitors had no impact on LVH prevalence.

The ~1 g/dl difference in mean Hb level between those with and without baseline LVH is statistically significant. However, it is important to note that the mean Hb levels in those with LVH at baseline are within the current guideline targets for dialysis.

![Graph](image1)

**Fig. 1.** Prevalence of cardiovascular disease in early renal disease (adapted from Culleton et al. [4]). CVD, cardiovascular disease; CAD, coronary artery disease; CHF, congestive heart failure; LVH, left ventricular hypertrophy; Rx, cardiac medications.

![Graph](image2)

**Fig. 2.** Baseline prevalence of left ventricular hypertrophy by degree of renal function and haemoglobin level (adapted from Levin et al. [5]).
patients. Studies in dialysis patients have previously shown that a sustained decrease in Hb level of 1 g/dl is associated with an increased risk of left ventricular dilatation, systolic dysfunction, chronic heart failure and death in dialysis patients [7].

A multivariate analysis showed that the risk of having LVH at baseline increased with age (odds ratio (OR) 1.019, 95% confidence interval (CI) 1.002–1.037 for every 1 year older) and systolic BP (OR 1.015, CI 1.004–1.02 for every 1 mm Hg increase) but decreased with female gender (OR 0.566, CI 0.340–0.943) and Hb level (OR 0.97, CI 0.966–0.9915 for every 0.1 g/dl increase).

LVH is defined on a population basis as LVMI > 130 g/m² for men or > 100 g/m² for women. This is, however, an arbitrary categorization of a continuous variable. A prerequisite for developing LVH is an increase in LVMI, i.e. LGV. Since LGV is a dynamic process that might start early in renal disease, it may be more clinically relevant to study LGV in this population. Significant LGV over a 12-month period was defined as either an increase of > 20% from baseline or an absolute increase of > 20 g/m² [8,9].

Further analysis of the same cohort over a 12-month period (n = 246 with evaluable echocardiograms) showed that there was no significant difference in baseline creatinine clearance, Hb or systolic BP in patients with vs without LGV over 12 months. However, the presence of LGV was associated with a significantly greater decrease in Hb and a significantly greater increase in systolic BP from baseline over this period. Indeed, multivariate analysis showed that only a decrease in Hb (OR 1.32, CI 1.1–1.59 for every 0.5 g/dl decrease) and an increase in systolic BP (OR 1.11, CI 1.02–1.21 for every 5 mm Hg increase) over 12 months, and baseline LVMI (OR 0.85, CI 0.76–0.96 for every 10 g/m² decrease), predicted LGV.

Clinical symptoms related to LVH tend to lag behind LVH development. Thus, given the short (12 months) period of evaluation, the proportion of patients (15%) experiencing progression of cardiac symptoms was relatively small. Patients with progression of cardiac symptoms (CCS/NYHA class) over 12 months were older, had lower renal function or lower Hb at baseline (Table 2). Perhaps more importantly, patients whose cardiac symptoms progressed over 12 months were those who experienced a significant fall in BP (mean arterial pressure and diastolic BP) and a significant increase in LVMI during this time.

In this study, a total of 23% of patients were hospitalized during the 12-month evaluation period; 22% of hospitalizations were related to cardiac causes and 24% due to renal causes. Baseline factors predictive of hospitalization were increased age, lower creatinine clearance, lower Hb and increased parathyroid hormone (Table 3). Other factors predictive of hospitalization were change in creatinine clearance (hospitalized patients had a significantly greater decline) and weight (weight loss in hospitalized patients vs weight gain in those not hospitalized); LVMI increased in hospitalized patients but regressed

Table 1. Predictors of LVH at baseline in patients with renal insufficiency

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline LVH status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVH− (n = 243)</td>
<td>LVH+ (n = 135)</td>
<td>P value</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>37.7</td>
<td>32.1</td>
<td>0.0010</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>13.0</td>
<td>12.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>141.3</td>
<td>150.3</td>
<td>0.0003</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>103.6</td>
<td>106.6</td>
<td>0.029</td>
</tr>
<tr>
<td>ACE inhibitor use (%)</td>
<td>52.1</td>
<td>45.1</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Table 2. Predictors of change in cardiac symptoms (CCS/NYHA class) over 12 months (Levin et al. [5])

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Progression of cardiac symptoms over 12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 175)</td>
<td>Yes (n = 31)</td>
</tr>
</tbody>
</table>
| At baseline
| Age (years) | 55 | 63 | 0.01 |
| Creatinine clearance (ml/min) | 37.9 | 31.6 | 0.05 |
| Hb (g/dl) | 12.9 | 12.2 | 0.06 |
| Over 12 months
| Change in LVMI (g/m²) | −0.6 | 4.96 | 0.34 |
| Change in MAP (mm Hg) | 0.89 | −5.2 | 0.01 |
| Change in diastolic BP (mm Hg) | 0.94 | −5 | 0.01 |

Table 3. Predictors of hospitalization over 12 months (Levin et al. [5])

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hospitalization over 12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 183)</td>
<td>Yes (n = 55)</td>
</tr>
</tbody>
</table>
| At baseline
| Age (years) | 55 | 60 | 0.04 |
| Creatinine clearance (ml/min) | 38 | 32 | 0.01 |
| Hb (g/dl) | 13.0 | 12.4 | 0.029 |
| Parathyroid hormone (median, pmol/l) | 8.2 | 11.2 | 0.008 |
| Over 12 months
| Change in LVMI (g/m²) | −1.33 | 6.63 | 0.07 |
| Change in creatinine clearance (ml/min) | −3.4 | −6.5 | 0.007 |
| Change in weight (kg) | 0.79 | −1.2 | 0.002 |
in those not hospitalized (difference approaching significance).

Interestingly, in a different retrospective cohort study performed in Canada, the authors demonstrated that the existence of anaemia in patients prior to dialysis is an independent predictor of hospitalization, after adjusting for baseline renal function [10]. This study examined baseline predictors of hospitalization in a cohort of 362 pre-dialysis patients in Canada. Multivariate analysis, after adjustment for baseline renal function, showed that advanced age (risk ratio (RR) 1.017), angina (RR 1.893), peripheral vascular disease (RR 1.545) and (lower) baseline Hb level (RR 0.987) were independent predictors of pre-dialysis hospitalization. Thus, many well recognized predictors of adverse outcomes among dialysis patients are also useful predictors of pre-dialysis morbidity.

Target haemoglobin levels in ESRD

Anaemia is a well recognized risk factor for CVD. The cardiovascular and neurohormonal effects of anaemia are both direct and indirect, and are sustained over time. It is important to remember that anaemia is really defined in terms of Hb levels below the normal physiological value, i.e. in men Hb < 14.5 g/dl and in women Hb < 13.5 g/dl. Therefore, the question arises of whether the current target Hb levels (>11 g/dl), according to both European and North American guidelines [6,11], are physiologically relevant. It should also be remembered that these targets have not been reviewed in patients prior to renal replacement therapy.

In the Canadian multicentre study cohort [5], the prevalence of anaemia increased as renal function declined. However, most importantly, not only did the prevalence of anaemia (defined as Hb < 13 g/dl) increase with progression of renal disease, but even at what many would consider very early kidney disease (creatinine clearance > 50 ml/min), 25% of patients had anaemia (Figure 3). This implies a long duration of exposure to a risk factor that is known to impact on eventual clinical outcome.

In both dialysis and early renal disease, evidence has accumulated showing that anaemia has a detrimental impact on ischaemic heart disease, LVH, quality of life, exercise capacity, cognition, hospital stay and mortality [7,10,12–16], although it should be noted that there are currently few data on its effect on mortality and cognition in early renal disease. More importantly perhaps, there is accumulating evidence that the treatment of modifiable risk factors such as hypertension, proteinuria, diabetes, smoking, and, to some extent, Hb levels, hyperparathyroidism and dislipidaemia, in renal disease can delay progression of both renal and cardiovascular disease.

Further evidence of the CVD burden of early renal disease was observed in a retrospective study of a French cohort of 748 ESRD patients [17]. The incidence of atherosclerotic arterial occlusive events was studied in these patients before and after initiation of dialysis. The results showed that 42% of first myocardial infarctions occurred prior to initiation of dialysis. The huge burden of CVD illness in early renal disease patients was confirmed by data from the Canadian Organ Replacement Registry, which showed that at the time of dialysis initiation, 89% had hypertension, 35% diabetes, 32% angina and 30% had had a myocardial infarction [18].

A problem with CVD and renal disease is determining which occurs first. It is established that renal function predicts poorer outcomes in the general population. However, CVD has also been shown to be associated with poorer outcomes in patients with renal disease. For example, in a study of 640 patients

![Graph showing prevalence of anaemia by degree of renal function at baseline](image-url)

**Fig. 3.** Prevalence of ‘anaemia’ by degree of renal function at baseline (adapted from Levin et al. [5]).
with ESRD and acute myocardial infarction, the 1 year mortality rate (53%) was approximately double that of acute myocardial infarction patients without evidence of renal impairment (25%) [19]. The presence of CVD also predicts time to dialysis in patients with early renal disease. Patients with a history of CVD and CVD symptoms at baseline were more likely to begin dialysis than those without symptoms [20].

Conclusions

In summary, the large burden of CVD in early renal disease is a result of multiple risk factors, and the risk factors for both CVD and progression of renal disease are similar. Although LVH is prevalent early in the process of progressive renal decline, it is associated with a number of modifiable risk factors (e.g. anemia and systolic BP). Anemia should be defined physiologically and it is important to remember that it is also associated with a number of CVD risk factors (e.g. LVH, coronary artery disease, CHF, etc.) that may or may not be independent of each other.

In the future, it is critical that steps are taken to ensure early identification of both renal disease and specific risk factors. Recognizing modifiable risk factors and addressing them early in the course of renal disease will facilitate the ultimate goal of improving patient outcomes, delaying not only the progression of early renal disease but also the progression of CVD.

References

8. Collins HW. Reproducibility of left ventricular mass measurements by two-dimensional and M-mode echocardiography. J Am Coll Cardiol 1989; 14: 672–676
18. Canadian Organ Replacement Registry, Canadian Institute for Health Information (CIHI), Don Mills, Ontario, Canada, 1999