Left ventricular hypertrophy: a surrogate end point or correlate of cardiovascular events in kidney disease?

Todd F. Griffith1, Donal N. Reddan1, Preston S. Klassen1 and William F. Owen1,2

1Duke Institute of Renal Outcomes Research and Health Policy, Department of Medicine, Duke University Medical Center, Durham, NC and 2Baxter International Healthcare, Waukegan, IL, USA

Keywords: anaemia; cardiovascular disease; end-stage renal disease; left ventricular hypertrophy; mortality

Surrogate endpoints vs clinical correlates

Prentice [1] offered a statistical definition of a surrogate endpoint as ‘a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint’. A National Institutes of Health (NIH) working group generated less quantitatively rigorous definitions that contrasted clinical and surrogate endpoints [2]. A ‘clinical endpoint’ is ‘[a] characteristic or variable that reflects how a patient feels, functions, or survives’, and so is related to the surrogate, ‘[a] biomarker that is intended to substitute for a clinical endpoint’. Moreover, ‘[a] surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence’ [2]. While Prentice’s definition of surrogate requires the surrogate to account for the entirety of the effect of an intervention on a clinical endpoint, the NIH definition is more lenient. There must be clear distinction between a surrogate endpoint and a correlate. While an appropriate surrogate necessarily correlates with a clinical endpoint, all correlates are not effective surrogates [3]. For example, fever is a clinical correlate of serious vascular access infection, but is not an adequate surrogate for demonstrating the ability of an intervention to attenuate access-related sepsis. So, all surrogate measures are clinical correlates, but the converse is far from true. Surrogate endpoints are attractive for clinical trials, especially if the surrogate outcome occurs sooner, more often, or is easier to measure. The medical literature is replete with examples of putative surrogates that have failed to adequately predict clinical endpoints [4,5]. For example, reducing ventricular ectopy does not necessarily correlate with improved mortality. In hindsight, these measures were clinical correlates alone. This sobering limitation has been observed even in situations in which a sound chain of logic supports the use of the measure as a surrogate.

Anaemia, left ventricular hypertrophy and mortality

Cardiovascular disease (CVD) is a serious problem in the end-stage renal disease (ESRD) population. Multiple authors have suggested that the risk for cardiovascular mortality in ESRD patients is established during chronic kidney disease (CKD) before renal replacement therapy [6,7]. Increasingly, anaemia, abnormalities in left ventricular (LV) geometry, especially LV hypertrophy (LVH) and cardiovascular morbidity and mortality have become inseparably linked in the nephrology literature [8–10]. Observational data support these associations. The chain of logic is as follows: (i) LVH defined by echocardiography has been described in 36% of patients with CKD [11] and 74% of incident ESRD patients [12]; (ii) LVH is associated with subsequent cardiovascular mortality in ESRD patients [13]; (iii) anaemia is a risk factor for LVH in patients with CKD [14] and ESRD [15] and a risk factor for de novo congestive heart failure (CHF) with ESRD [16]; (iv) regression of LVH results in a reduction in cardiovascular morbidity events in hypertensive patients without ESRD [17]; (v) anaemia correction will lead to regression of LVH and/or less CHF; and, therefore, (vi) cardiovascular outcomes in patients with CKD progressing to ESRD will be improved by anaemia correction. This syllogistic reasoning pre-supposes LVH as an attractive surrogate endpoint for cardiovascular morbidity and mortality in trials of anaemia correction. How sound is this contention? Is the relationship between anaemia correction and LVH suitably defined? Is there adequate evidence supporting LVH as a surrogate endpoint for cardiovascular morbidity or mortality in this population? We will attempt to answer these questions and provide a conceptual framework for intervention trials.
Anaemia treatment and clinical outcomes

The timing and magnitude of pharmacologic therapy of anaemia in CKD and ESRD patients is unclear. Erythropoietins (Epo) are effective in treating the anaemia of CKD. The benefits of anaemia correction with Epo in this population include improved cognitive and physical function resulting in improved health-related quality of life [18] and, possibly, slowing CKD progression [19]. More substantive outcome data is lacking.

Anaemia is associated with mortality and hospitalization in ESRD [20]. Treatment of anaemia with Epo in ESRD is associated with desirable outcomes including improvements in quality of life [21], exercise tolerance [22], immune [23], cognitive [24] and sexual function [25], and reduced hospitalization frequency [26] and exercise-induced cardiac ischaemia [22]. However, the degree of anaemia correction conferring optimal mortality benefit is less certain, and anaemia correction has not been directly shown to confer mortality benefit in either CKD or ESRD. The Normalization of Haematocrit Trial evaluated the effects of partial vs complete haematocrit correction with Epo in a cohort of 1233 haemodialysis patients with a previous history of congestive heart failure or ischaemic heart disease [27]. In this randomized, controlled trial (RCT), patients assigned to the haematocrit of 42% reached the primary outcome, death or myocardial infarction, more often than those patients randomized to maintain a haematocrit of 30%. Although this difference did not reach statistical significance, the trial was discontinued early, when there was no likelihood of demonstrating that randomization to the normal haematocrit group could induce beneficial results and the experimental group had a significantly increased rate of vascular access thrombosis. Although a cross-sectional analysis demonstrated that patients with higher haematocris in each group had better outcomes, post hoc analyses of this sort may be confounded by survival bias. This study suggests that the benefits of anaemia correction in dialysis patients with pre-existing heart disease are limited. Whether these findings are generalizable to haemodialysis patients without clinical heart disease, peritoneal dialysis patients or CKD patients remains undetermined.

Findings from non-randomized interventions and retrospective observational studies, with their attendant biases, support the contention that ESRD patients might benefit from haematocrit values greater than the 33–36% goal range proposed by the National Kidney Foundation (United States) [28]. For example, Pickett et al. [29] noted improvements in multiple neurophysiologic parameters after raising mean haematocrit values from 32 to 43% in a cohort of dialysis patients. In haemodialysis patients with no CVD, Moreno et al. [30] demonstrated that achievement of a mean haematocrit level of 38.5% led to improvements in functional status and quality of life. A recent observational study by Collins et al. [31] revealed lower hospitalization rates and expenditures for incident dialysis patients with haematocrit values ≥36% compared with patients with values of 33–36%.

LVH as a surrogate outcome in anaemia correction

Surprisingly, in the absence of strong, consistent and substantial data demonstrating mortality benefits of anaemia correction for patients with CKD or ESRD, LV geometry has implicitly been proposed as a surrogate outcome. This scientific and clinical strategy seems curious in light of the paucity of intervention studies demonstrating that anaemia correction improves clinical events in parallel with a predictable change in LV geometry and/or function.

In uncontrolled intervention studies, investigators have suggested variable reductions of LVH during anaemia treatment with Epo in ESRD patients [22,23]. However, the designs of these studies do not support the establishment of causal relationships between anaemia correction and regression of LVH. In a more rigorously designed study, Foley et al. [33] randomized haemodialysis patients with echocardiographically defined cardiomyopathy (categorized as LVH based on an elevated LV mass index or LV dilatation based on an elevated LV volume index) to Epo-corrected haemoglobin levels of 9.5–10.5 or 13–14 g/dl. No regression of concentric LVH or of LV dilatation resulted from normalization of the haemoglobin concentration, although the cardiomyopathy may be too advanced at this stage for benefit from anaemia correction. Moreover, the study may not have been adequately powered for these outcomes (type 2 error). These results do not support the proposed chain of events: that anaemia correction may lead to amelioration of LVH and a subsequent reduction in mortality. Data on the relationship of LVH and anaemia is similarly sparse in CKD patients. Two groups describing outcomes for a total of 20 patients reported regression of LVH in association with Epo treatment of anaemia [34,35]. Both of these intervention studies were uncontrolled, so the effect of other parallel processes of care cannot be dismissed. There are no studies reporting clinical cardiovascular endpoints, other morbidities, or mortality with anaemia correction in CKD patients.

The aforementioned chain of logic relies on anaemia correction as the pivotal strategy to improve CV morbidity and mortality. Therefore, it makes an a priori assumption that the majority of the CV risk is causally a function of anaemia. If the preponderance of the relative risk is from anaemia, then abrogating anaemia should reduce LVH and death risk in parallel. However, LVH may be a correlate of CV disease wholly independent of anaemia. Alternatively, LVH may be provoked by concurrent processes associated with the development of CKD/ESRD, in addition to anaemia. In CKD/ESRD patients, hypertension is one likely candidate. This is substantiated by the observations that systolic blood pressure is both predictive of LV growth in CKD patients [14] and correlated with degree
of LVH in ESRD patients [36]. Additional associations with LVH in ESRD patients include hypoalbuminemia [37], nocturnal hypoxaemia [38], plasma renin activity [39], hyperparathyroidism [40] and endothelin levels [41]. Last, regression of LVH has been observed in some kidney transplant recipients [42], which may be a consequence of the re-establishment of euvoelaemia. So, changes in LV geometry in CKD and ESRD are likely to be multifactorial. Therefore, correcting anemia may confer clinical benefits that will not be detected by changes in LV geometry.

Conclusions

The majority of evidence gathered to date on anemia, LVH and cardiovascular outcomes in CKD and ESRD patients has established a variety of predictable as well as unanticipated associations. As the presence of LVH is a poor prognostic sign, attempts to prevent its development seem prudent. However, the caveats regarding surrogate outcomes must be kept in mind in trial design and interpretation. The simple demonstration of reduction of LVH with Epo treatment of anemia should not lead to the unequivocal inference that anemia correction will result in survival benefit in these populations. Conversely, the absence of a change in LV geometry with anemia correction does not necessarily lead to the inference that intensified management of anemia does not confer a survival benefit. Genuine clinical endpoints, like mortality, and readily adjudicated clinical events, like hospitalizations, should remain our gold standard for proof of efficacy in the quest to unruavel the Gordian knot linking anemia, LVH and cardiovascular morbidity and mortality. In the absence of measureable clinical events, alterations in LV geometry and/or function alone may offer imperfect but important alternative measures for scrutiny. Moreover, studies, which use intermediate measures like LVH, may provide insights into disease pathobiology. As is being seen in some contemporary intervention trials, future clinical studies should be designed to address the shortcomings of our current knowledge, recognizing that LV geometry is most appropriately regarded as a correlate of the complicated milieu in CKD and ESRD.

Conflict of interest statement. D.N.R. receives research support from and is a speaker for Ortho Biotech, Inc., which markets epoetin alfa. P.S.K. is employed by Amgen, Inc., which manufactures and markets darbepoetin alfa and epoetin alfa. This work was completed while P.S.K. was a faculty member at Duke University. W.F.O. is Chief Scientist for Baxter International Healthcare, Renal, which markets epoetin omega.

References

Icodextrin-associated peritonitis: what conclusions thus far?

Eric Goffin1, Jean-Pierre Cosyns2, Françoise Pirson3 and Olivier Devuyst1

1Division of Nephrology, 2Division of Pathology and 3Division of Pneumology, Université Catholique de Louvain Medical School, Brussels, Belgium

**Keywords:** allergy; hypersensitivity; icodextrin; peritonitis; peritoneal dialysis; peptidoglycan

**Introduction**

Icodextrin 7.5% (Extraneal; Baxter Healthcare, McGaw Park, IL, USA) is an iso-osmolar formulation of maltodextrin glucose polymer derived from starch that is increasingly used to enhance ultrafiltration during long dwells in continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) patients [1–3]. Since its introduction in the UK in 1994, icodextrin has been used in more than 23 000 patients in many parts of the world [4]. Except for rare cutaneous hypersensitivity reactions [5,6], icodextrin is generally safe and well tolerated. Within the last 3 years, however, several reports of sterile chemical peritonitis have been attributed to icodextrin prescription [7–19]. In this comment, we will briefly review the clinical and physiopathological aspects of this syndrome.

**Clinical presentation of icodextrin-associated peritonitis**

Typically, peritoneal dialysis (PD) patients with icodextrin-associated sterile peritonitis are admitted with abdominal discomfort and cloudy dialysate effluents. No associated rash, fever or other hypersensitivity...