

# Cardiorenal syndrome: one disease – two paths?

A report from the fourth Annual Scientific Meeting of the Cardiorenal Forum.



## Introduction

That renal and cardiac disease appear inseparable from an epidemiological perspective is unsurprising, since they share many risk factors, notably hypertension, diabetes and inflammation. To date, however, our focus on the disparate specialities of 'cardiology' and 'nephrology' has reinforced a perception of each system as separate. The Cardiorenal Forum (CRF) was established to challenge this perspective.

The most recent meeting, last autumn, 'Optimising care at the cardiorenal interface' was organised by the Royal College of Physicians, the British Cardiovascular Society and the Renal Association, in association with the CRF. The meeting sought, first to reconsider the relationship between renal function and cardiovascular outcome, and to explore the current state of management of kidney disease with a particular focus upon haemodialysis. Sessions also examined the association between renal dysfunction, heart failure and diuretic resistance, and the need for integration across healthcare boundaries to address these increasingly prevalent conditions.

## Epidemiology and eGFR

The prevalence of end-stage renal disease is rising, due increasingly to reno-vascular disease and type 2 diabetes; perhaps reflecting ageing populations and better management of elevated blood pressure. As renal function deteriorates, the rate of cardiovascular events rises.<sup>1</sup>

To improve awareness of renal disease in the general population requires a reliable assessment of renal function. Serum creatinine, although widely available, is unreliable. Creatinine rises only in established renal disease, thus relatively normal levels may provide false reassurance. This can be partially 'corrected' by using the reciprocal of serum creatinine. More

recently, estimation of glomerular filtration rate (eGFR), using either the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) formulae has been shown to more closely reflect directly measured creatinine clearance.<sup>2</sup> Both methods suffer practical confounding through differential correction for age and female sex, the inclusion of weight in the Cockcroft-Gault formula and of age in MDRD. In addition, eGFR rises in the first decade of nephropathy reflecting hyperfiltration. The detection of microalbuminuria during this early phase of hyperfiltration may more accurately define early renal impairment. Thus, while eGFR may be above the typical watershed of 60 ml/min, the presence of microalbuminuria defines stages I and II of chronic kidney disease (CKD).

Once eGFR falls below 60 ml/min, cardiovascular risk accelerates, although the strength of this association is markedly reduced when corrected for a full range of cardiovascular risk factors.<sup>3</sup> It is, thus, unclear whether renal impairment is intrinsically a risk factor in cardiovascular disease or merely reflects a collated risk factor burden. It remains the case, however, that the lower the eGFR the greater the likelihood of adverse outcome in patients following myocardial infarction<sup>4</sup> and in patients with heart failure.<sup>5</sup>

The mainstay of treatment in patients with renal impairment is inhibition of the renin-angiotensin system (RAS). While there is strong evidence for benefit across a range of cardiovascular disease, recent studies suggest a threshold for effect, with loss of benefit,<sup>6</sup> and possibly harm,<sup>7</sup> at lesser degrees of renal impairment (eGFR >60 ml/min). In the presence of microalbuminuria, RAS inhibition may reduce the rate of progression of proteinuria, however, the evidence-base is more disparate. It is uncertain if delaying progression of proteinuria delays progressive renal impairment; again a threshold effect may also exist at lesser levels of microalbuminuria.<sup>8</sup>

The inclusion of the measurement of eGFR within the Quality Outcomes Framework (QOF) has increased awareness and reporting of renal disease within primary care, with some evidence of increased early referral to specialist care. Attention has simultaneously been drawn to the limitations of eGFR. To obviate at least part of the problem with the age dependence of estimation of eGFR by MDRD, CKD stage III has recently been subdivided into III (a) and III (b) at an eGFR of 45 ml/min.

## Service organisation

An increased awareness of renal impairment coupled with the mantra that CKD is "one piece of a vascular jigsaw" that includes diabetes, hypertension and cardiovascular disease is a heady combination. Awareness of the problem does not, however, equate with effective treatment, which requires much better integration of services than "our focus on structures and not on the patient" allows. In outlining the "primary care home" where "if fulfilled, our policies are taking us", David Colin-Thome provided an ambitious vision of integration (not only of primary and secondary care but of social services), which may well be a necessary realisation of the financial straits that we approach. At present, however, such idealism seems to sit uncomfortably alongside the fragmentation of primary care into isolated commissioning and provider ventures, of commissioning into primary care trusts (PCTs) and consortia, and of community services into units run by various external agencies.

When the dust settles, perhaps truly integrated local services will exist (no longer a primary/secondary divide?) with clinically driven disease management programmes capable of dealing with the growing burden of chronic disease, such as heart failure. For, in an ageing population, it is in heart failure

## MEETING REPORT

that the entanglement of chronic kidney and vascular disease reaches its apogee.

## Heart failure

The association between heart failure and renal impairment is well recognised with over 30% of patients in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) study population having an eGFR of <60 ml/min. In those with an eGFR of <30 ml/min the primary outcome of cardiovascular death or heart failure hospitalisation was three times more common.<sup>5</sup> This association was present irrespective of the ejection fraction. While it is relatively straightforward to envisage decreased renal perfusion as a consequence of reduced cardiac output in patients with systolic left ventricular dysfunction, this does not, however, explain the association between renal impairment and failure in those with preserved ejection fraction. This latter population is expanding, and frequently presents to hospital with oedema, which, in my experience, becomes increasingly intransigent as renal function deteriorates.

Although refractory oedema is well recognised in patients with established heart failure, therapeutic options remain markedly limited. Provided there is good adherence to treatment and no conflicting therapeutic (non-steroidal anti-inflammatories or calcium channel blockers) or physiological (anaemia or hypothyroidism) explanation, then diuretics remain the mainstay of treatment. Based principally upon clinical observation, diuretic infusion is probably more effective than bolus doses. With due diligence, 'sequential nephron blockade' (the targeting of multiple sites of action with the combination of loop and thiazide diuretics as well as spironolactone)

may also help diuresis in refractory cases. Sadly, recent clinical studies of intravenous dopamine, natriuretic peptide infusion or of oral adenosine or vasopressin antagonists have all been unsuccessful. For refractory oedema there remains ultrafiltration,<sup>9</sup> which may best have a role in younger patients (<70 years) who lack evidence of substantial renal dysfunction. Care needs to be taken not to 'over-diurese' the patient. The possibility of peritoneal dialysis is being explored.

## Dialysis

Once established, decline in renal function is inexorable. No effective intervention has yet been found to halt this progression with both the correction of renal artery stenosis and high-dose statin recently disappointing. When end-stage renal disease is reached, only dialysis or transplantation remain. Dialysis, which is increasingly performed, has been shown to place an immense haemodynamic insult upon the cardiovascular system, accounted for predominantly by the maximum drop in blood pressure and the volume of filtrate removed during the procedure.<sup>10</sup> In addition, dialysis produces substantial, cumulative myocardial stunning and dysfunction, and induces a strong, systemic inflammatory response. Interestingly, it has been suggested that frequent low-grade troponin release might even encourage the development of auto-antibodies to troponin and an 'auto-immune carditis'. The possibility of 'gentler' dialysis is being explored, with the goal of reduced blood pressure changes and filtrate volume through frequent, possibly domestic, nocturnal dialysis. Although sudden death occurs in 7% of this population, the underlying reasons are unclear. Whether

there might be a specific role for implantable defibrillators is not known.

## Conclusion

Our understanding of the relationship between chronic renal and cardiovascular disease is, as yet, elemental, and based more on observation and empirical enquiry than on scientific study.

Whilst helpful in raising awareness of renal impairment, eGFR remains confounded by age and body mass. Therapies to prevent progression of renal disease are lacking. Although the mainstay of treatment in the later stages of renal disease, it seems likely that dialysis is itself a strong cardiovascular risk factor. We are left with one single clinical intervention – early detection and treatment of elevated blood pressure.

There is obviously a great need for further research, which is now being addressed by the recently established Cardio-Renal Trial Group. Perhaps the greatest paradox is that patients with renal impairment have been excluded from cardiovascular studies for so long. This needs to be challenged. In closing the meeting, Professor Roger Boyle (National Director of Heart Disease and Stroke) commented on the "huge interaction" between cardiovascular and renal disease, and wondered "why we have gone down different paths for so long" ●

### Hugh McIntyre

Consultant Cardiovascular Physician

East Sussex Hospitals Trust

(Hugh.McIntyre@esht.nhs.uk)

**For more information on the Cardiorenal Forum and future events, see [www.cardiorenalforum.com](http://www.cardiorenalforum.com)**

## References

- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–305.
- Verhave JC, Gansevoort RT, Hillege HL, De Zeeuw D, Curhan GC, De Jong PE. Drawbacks of the use of indirect estimates of renal function to evaluate the effect of risk factors on renal function. *J Am Soc Nephrol* 2004;**15**:1316–22.
- Manjunath G, Tighiouart H, Ibrahim H *et al*. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003;**41**:47–55.
- Anavekar NS, McMurray JJ, Velazquez EJ *et al*. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;**351**:1285–95.
- Hillege HL, Nitsch D, Pfeffer MA *et al*. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006;**113**:671–8.
- Solomon SD, Rice MM, Jablonski KA *et al*. Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the prevention of events with ACE inhibition (PEACE) trial. *Circulation* 2006;**114**:26–31.
- Yusuf S, Teo KK, Pogue J *et al*. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–59.
- Asselbergs FW, Diercks GF, Hillege HL *et al*. Effects of foscipril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 2004;**110**:2809–16.
- Costanzo MR, Guglin ME, Saltzberg MT *et al*. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49**:675–83.
- Wehle B, Asaba H, Castenfors J *et al*. Hemodynamic changes during sequential ultrafiltration and dialysis. *Kidney Int* 1979;**15**:411–18.