MEETING REPORT

The failing heart and kidney

The interest in the increasing overlap between cardiac and renal disease was shown by a well-attended meeting, 'The failing heart and kidney', organised by the Cardiorenal Forum. Over 100 nephrology and cardiology consultants/trainees, specialist nurses and other health personnel with a special interest in this field attended the meeting at the British Academy, London, on 11 July 2008.

CARDIORENAL FORUM

Cause or effect

The meeting set off to a stimulating start with Dr Alan Jardine (Consultant Nephrologist, Western Infirmary, Glasgow) providing an interesting epidemiological overview on cardiorenal disease. The increasing prevalence of chronic kidney disease (CKD) comes hand-in-hand with a growing cardiovascular disease (CVD) burden. Patients with progressive renal disease are known to have an increased risk of CVD. However, the pattern of outcomes and the relationship with risk factors are somewhat different from the general population. CVD accounts for 50% of mortality in endstage renal disease (ESRD). While there have been several studies assessing the impact of reduced estimated glomerular filtration rate (eGFR) on cardiovascular outcome, the key question remains whether CKD causes CVD or *vice versa*.

Previous views have held that the existence of common risk factors like hypertension, smoking and hyperlipidaemia explained the close association between CVD and CKD, but evidence now points towards a more complex relationship between the two entities. ESRD leads to hyperlipidaemia, inflammation and malnutrition, all of which may contribute to atheromatous coronary artery disease. ESRD in itself also causes uraemic cardiomyopathy, left ventricular hypertrophy, myocardial fibrosis and fatal arrhythmias.

Dr Jardine also highlighted the close association between chronic heart failure and CKD. Neurohormonal activation secondary to diminished renal perfusion and subsequent impaired function resulting in the entity of cardiorenal syndrome in heart failure was also discussed.

Neurohormones

Dr Mike Schacter (Senior Lecturer, Department of Clinical Pharmacology, St Mary's Hospital, London) went on to explore in detail the role of neurohormonal activation in heart failure and a systematic overview of the natriuretic peptide/kinin systems. Heart failure is not just pump failure, but a systemic syndrome with complex neurohumoral, inflammatory and metabolic responses. All drug interventions that have improved outcomes in heart failure have interacted with these neurohumoral responses. Activation of the renin–angiotensin system (RAS) results in structural (loss of proximal convoluted tubules [PCT] and fibrosis) and functional (reduction of PCT flow/oxidative stress) changes leading to hypoxia of the kidney and subsequent ESRD as a result of tubule interstitial injury.

Dr Iain Squire (Senior Lecturer, Cardiovascular Sciences, Leicester) shed further light on the importance of renin–angiotensin–aldosterone system (RAAS) blockade in heart failure by separately analysing their roles in reduced and preserved ejection fraction. Most of the evidence base is undoubtedly in heart failure with reduced ejection fraction. Data from several long-term randomised-controlled trials (SAVE, AIRE, TRACE, SOLVD showed unequivocal benefit with the use of angiotensin-converting enzyme (ACE) inhibitor therapy resulting in reduction in mortality and re-admission, as well as re-infarction. The wealth of evidence led to the National Institute for Health and Clinical Excellence (NICE) spelling out in its heart failure guidelines that all patients with heart failure due to left ventricular dysfunction should be considered for treatment with an ACE inhibitor, with emphasis on the need to achieve optimal tolerated/target doses.

The evidence is not as clear in heart failure with preserved ejection fraction, and the question arises: what are we treating? Some studies have questioned whether patients with suspected heart failure and preserved left ventricular systolic function suffer from diastolic heart failure or from misdiagnosis. While there is unequivocal evidence in heart failure for RAAS inhibition in the presence of impaired left ventricular systolic function, this is currently much less convincing in heart failure with preserved left ventricular systolic function.

Controlling risk factors

Dr Philip Kalra (Consultant Nephrologist, Salford Royal Hospital, Salford) proceeded to demystify the kidney and the classifications of CKD currently available. The prevalence of CVD in CKD dramatically worsens once the eGFR falls below 60 ml/minute. Studies have clearly shown that the rates of death and cardiovascular death rose with the decline of renal function, with cardiovascular mortality rates being much higher among dialysis patients. Left ventricular hypertrophy, calcification of coronary arteries, uraemic arteriopathy/atherosclerosis were all earmarked as contributing factors. The most significant risk factors associated with the progression of CKD include hypertension and proteinuria, and as such, treatment should be directed towards controlling them.

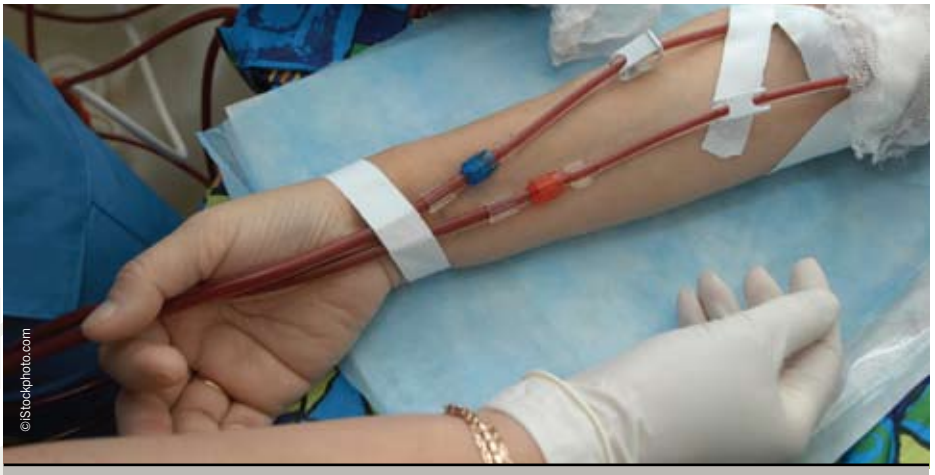
Meta-analysis of several randomised-controlled trials have highlighted the relationship between systolic blood pressure and increased risk of CKD, with evidence of slower decline in renal function with lower blood pressure goals. The drugs of choice for blood pressure control in CKD would be ACE inhibitors, angiotensin receptor blockers (ARBs) and selective renin inhibitors, like aliskiren, aiming to achieve

target blood pressures of 125/75 mmHg in patients with proteinuria and 130/80 mmHg in all others. In patients with diabetes, suboptimal blood pressure control results in GFR loss of 8–16 ml/min/year and with tight blood pressure control, this falls to as little as 1–2 ml/min/year. (Age-related decline in GFR in a normal individual is 1 ml/min/1.73 m^2 after 30 years).

Dr Kalra emphasised that it is common to see deterioration in renal function with RAAS blockade in patients with congestive heart failure, and up to 25% increase in creatinine is acceptable. Higher values may be acceptable in patients with severe congestive cardiac failure. If significant changes occur, reducing the diuretic dose and repeating biochemistry after 10 days, may permit continuation. A minority of these patients will have functionally significant atherosclerotic renovascular disease (ARVD). It was interesting to note that at Salford Royal Hospital, 51% of 527 ARVD patients receiving or previously treated with RAAS blockade, and only 8% were intolerant, thus breaking the myth that the presence of ARVD is a contraindication to RAAS blockade.

Diabetic nephropathy

Dr Marc Evans (Consultant diabetologist, Llandough Hospital, Cardiff) gave an in-depth account of the management of diabetic nephropathy, highlighting the need for collaborative combined care of patients by diabetologists and nephrologists. The challenge of diabetes is ever rising with about one million patients with diabetes still being undiagnosed nationally and diabetic nephropathy contributing to 50% of new dialysis patients. Managing diabetics costs the National Health Service (NHS) about £5 billion *per annum* (8–10% of total healthcare costs) and 80% of the costs are related to diabetes complications. Dr Evans highlighted the superiority of albumin–creatinine ratio (ACR) over protein–creatinine ratio (PCR). ACR is seen as the gold-standard testing for urinary albumin and although PCR measures total protein and is useful for patients with proteinuria, it is not accurate enough to determine microalbuminuria. ACR should be measured annually in diabetics, cut-offs being >2.5 in males and >3.5 in females. An ACR >10 suggests persistent microalbuminuria and >30 nephropathy. Once CKD stage 3 sets in, six-monthly monitoring of GFR is required and three-monthly in stages 4 and 5.



The onset of microalbuminuria and proteinuria in patients with type 2 diabetes increases the risk of progression to endstage renal disease

The progression of renal disease in type 2 diabetes is accelerated by the onset of microalbuminuria with the onset of proteinuria marking a steep decline of renal function and progression to ESRD. Cardiovascular mortality correlates with the severity of microalbuminuria in type 2 diabetes. Preventing renal disease in diabetes by tighter glycaemic control and optimising blood pressure (UKPDS group 1998) showed a significant reduction in microvascular end points, but not as much in macrovascular complications. The management of stable CKD would, therefore, involve meticulous blood glucose control, regular measurement of renal function (eGFR), lifestyle changes, aspirin, and tight blood pressure, as well as lipid, control.

Optimal blood pressure control will often require combination therapy. However, the strongest data for improving outcomes (both mortality and renal) are with RAS antagonists and in particular ARBs. Dr Evans highlighted that in Irbesartan in Diabetic Nephropathy (IDNT) and Irbesartan in Type 2 Diabetics with Microalbuminuria (IRMA-2), treatment with irbesartan was associated with a reduction in primary end points independent of blood-pressure lowering effects.

Global risk reduction

The keynote lecture delivered by Dr Kausik Ray (BHF International Fellow and Consultant Cardiologist at Addenbrooke's Hospital) focused on the global risk reduction of CVD. While cardiovascular mortality has declined in the UK, with improved survival in myocardial infarctions and acute coronary syndromes, the burden of coronary heart disease (CHD) is increasing. On a global scale, by 2020, CHD and stroke are projected to become the leading cause of death and disability worldwide, with mortality from CVD increasing to 20 million. Atherosclerosis is believed to begin as early as in teenage years. Low-density lipoprotein (LDL) increases throughout childhood and young adulthood, and with age, high-density lipoprotein (HDL) becomes less protective. Hence, low HDL in youth is of concern. The added protective effect of HDL seen in women is lost after the age of 70. Even when high-risk primary prevention patients are treated, two thirds of events are still missed.

Dr Ray then proceeded to explore each risk factor and the evidence-based treatment strategies available. Meta-analyses of intensive statin therapy studies and dyslipidaemia trials all point towards the benefit of lowering cholesterol with statins, irrespective of cholesterol levels.

Ongoing data analysis by Dr Ray highlights that higher HDL is associated with a reduction in CHD and ischaemic stroke. Treatment strategies for increasing HDL and reducing triglycerides include smoking cessation, regular

aerobic exercise, weight reduction and optimal diabetes control, as well as the use of drugs like statins, fibrates, niacin, metformin, etc.

The concept of the lower the better for cholesterol/LDL is certainly applicable to blood pressure as well. The risk of CHD mortality doubles with every 20 mmHg rise in blood pressure at any age. Data from a number of trials have suggested that perhaps the mode of lowering blood pressure is also important. The current hypertension guidelines by NICE recommend ACE inhibitors for patients younger than 55 years and calcium channel blockers/diuretics in those older than 55 or Afro-Caribbean patients of any age. Where monotherapy fails, a drug from the other group is added and many patients require all three drugs in combination. The keynote lecture ended on the note that a multifactorial approach was the need of the hour in the drive to combat the burgeoning global burden of CVD.

ACE inhibitors versus ARBs

The day's session, punctuated by informative discussions between talks and good audience participation, concluded with a debate, with the motion 'ACE inhibitors and ARBs are interchangeable in cardiorenal disease'. Dr Albert Ferro (Reader Cardiovascular Pharmacology, King's College London) proposed the motion based on the similar mechanisms of action between the two drugs, as well as the absence of difference in outcome in studies where both drugs were used together. ACE inhibitors in addition to preventing the conversion of angiotensin I to II also prevent the breakdown of bradykinin to inactive peptides. ARBs on the other hand selectively block the AT_1 receptors, leaving AT_2 unopposed. Studies have shown bradykinin antagonists to have no effect on blood pressure, left ventricular hypertrophy or any cardiovascular effect, suggesting no added benefit by inhibiting the bradykinin breakdown pathway. According to Dr Ferro, no significant difference in all-cause mortality or primary outcome was seen in the Valsartan in Acute Myocardial Infarction (VALIANT) trial (captopril, valsartan and the combination) or the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) trial, hence ruling out superiority of either class of drug. While ARBs certainly cause less angioedema, in his opinion, that certainly was not a strong enough reason to prevent them being interchangeable.

Dr David Bennet-Jones (Consultant Nephrologist, UHCW, Coventry) made a convincing counter argument on the grounds that, in addition to there being an inter-patient heterogeneity of response, benefits seen in some trials when used in combination suggest that the two drugs have different pharmacological effects.

Following a lively discussion by both speakers, a final show of hands proved a tilt in audience opinion and a clear win in favour of the opposition.

The take home message from this highly informative and enlightening day was that cardiorenal disease is a growing health problem and it is, thus, the need of the hour that general practitioners, nephrologists, diabetologists, cardiologists and whoever else may be involved in patient care, work in close unison. The point of contact for the patient may vary, but the unifying factor remains the predisposition to vascular disease and its subsequent complications. By maintaining a vigilant approach and optimising treatment, CKD can be stabilised and the onset of cardiovascular complications held at bay

Conflict of interest

The meeting was supported by an unrestricted educational grant from Sanofi-Aventis and Bristol-Myers Squibb Pharmaceuticals Limited.

Donah Zachariah,
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Correspondence

10 steps before you refer for hypertension

Dear Sirs

I felt that '10 steps before you refer for hypertension' was a good article but given that point 1 was "check that the measurement is correct", why on earth would you have a picture of an aneroid sphygmomanometer on the front cover when these are known to be inaccurate?

Yours faithfully

Peter Sever
Professor of Clinical Pharmacology and Therapeutics,
Imperial College London

The authors' reply

This is a well-made point and you are, of course, quite right. The picture was chosen for visual impact rather than as a recommendation. Aneroid sphygmomanometers are only accurate when new or after recalibration, which is recommended every six months. They rely on a coiled spring which loosens with each use. The authors do not recommend their routine use in practice.

Terry McCormack
Whitby Group Practice, Whitby

Francesco Cappuccio
Warwick Medical School, Coventry