Risk factors and metabolic mechanisms in the pathogenesis of uraemic cardiac disease

Sunil Bhandari

Department of Renal Medicine, Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, Kingston-upon-Hull, United Kingdom

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1. ABSTRACT

Chronic kidney disease has been increasingly recognized as a risk factor for incident heart failure. Despite advances in chronic heart failure treatment, the prognosis remains poor. The annual mortality from all cardiovascular causes in the end stage renal disease population is significantly higher than the general population, accounting for more than half of all deaths in this group. The mechanisms underlying the enhanced susceptibility to myocardial ischemia in chronic kidney disease are not well defined. Traditional cardiovascular risk factors, although common in chronic kidney disease, do not exert the same impact as in the general population. The presence of “renal-specific” non-traditional risk factors including endothelial dysfunction, inflammation, oxidative stress, anaemia, proteinuria and changes in vitamin D metabolism (encompassing the complex interactions of calcium and phosphate metabolism, hyperparathyroidism and vascular calcification) play an important role in cardiovascular disease progression. An increased understanding of the array of metabolic changes/adaptations occurring in uraemic heart disease have allowed one to consider optimal management strategies and to develop new strategies for future management of uraemic heart disease.

2. INTRODUCTION

In recent years the extent and significance of chronic kidney disease (CKD) has been increasingly recognized as a risk factor for incident heart failure (1). In the United States almost 13% of the population have evidence of renal damage (estimated glomerular filtration rate (eGFR) less than 60mls/min and/or proteinuria) (2), while in the United Kingdom at least 7% of the adult population have an eGFR of less than 60mls/min (3) and over forty thousand patients are receiving treatment for end stage renal disease (ESRD), a figure which continues to increase at 5% per annum (4).

Despite advances in the treatment of chronic heart failure (CHF), the prognosis remains poor (5). The prevalence of kidney dysfunction in the context of cardiac failure is about 25% (6, 7), while the prevalence of heart failure (related to cardiac disease rather than fluid overload) is around 31-40% in patients with ESRD (8-10). The syndrome of heart failure starts from impairment of cardiac function, a reduction in ejection fraction with subsequent inadequate tissue perfusion and arterial under-filling. This leads to compensatory mechanisms resulting in salt and water retention and subsequent increased venous pressure and capillary leak leading to oedema. This vicious cycle
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Table 1. Summary of classical, renal specific and other risk factors in uraemia for cardiovascular disease and heart failure (45, 203)

<table>
<thead>
<tr>
<th>Cardiac Risk Factors In Uraemia</th>
<th>Classical</th>
<th>Renal Specific</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Volume overload</td>
<td>Hyperhomocysteinaemia</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>Arteriovenous fistula</td>
<td>Sympathetic hyperactivity</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>Hyperparathyroidism</td>
<td>Oxidative stress/endothelial dysfunction</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Metabolic acidosis</td>
<td>Chronic inflammation</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Uraemic toxins-middle molecules</td>
<td>Hypoalbuminaemia-malnutrition</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Anaemia – erythropoietin stimulating agents</td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Functional iron deficiency</td>
<td>signalling pathways Akt/PIP3 GLUT 4</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Carnitine deficiency</td>
<td>Arterial stiffness</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>Reduced adiponectin</td>
<td>Vascular calcification</td>
<td></td>
</tr>
<tr>
<td>Hyperphosphataemia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vitamin D deficiency</td>
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</tbody>
</table>

results in the neurohormonal imbalance between vaso-dilatory factors (salt and water excretion) and vaso-constrictory factors causing salt and water retention. Even modest decreases in eGFR are associated with increased risk of death in patients with cardiac dysfunction, suggesting that renal dysfunction (RD) is an important additional co-morbid risk factor (11, 12). Impaired renal function is a recognized marker of severity of vascular disease (13), and patients with chronic renal insufficiency carry one of the greatest burdens of cardiovascular disease, which frequently leads to death before dialysis requirement is reached (14, 15). Indeed the annual mortality from all cardiovascular causes in the ESRD population is significantly higher than the general population at all ages (16), accounting for more than half of all deaths in this group (5, 7, 10).

Ischaemic heart disease (IHD) is highly prevalent in the uraemic population, and mortality following myocardial infarction increases with the degree of renal dysfunction (7, 17). However the mechanisms underlying the enhanced susceptibility to myocardial ischemia and subsequent morbidity and mortality in CKD are not well defined. High mortality rates were considered a result of accelerated coronary artery disease (18), but the incidence of symptomatic IHD far outweighs the incidence of angiographic coronary stenosis (19). Death from ‘classical’ myocardial infarction is not more common in uraemic patients (20) and autopsy studies have shown that classical coronary atherosclerosis is similar in renal failure patients in comparison to the age matched general population (20, 21). Interestingly uraemic vessels display medial thickening and calcification that leads to an increase in arterial stiffness and decreased compliance (22, 23). Hence the ‘traditional’ risk factors for cardiovascular disease, although still common in CKD, do not exert the same impact as in the general population. Reduced eGFR may therefore create a metabolic milieu conducive to promoting IHD and CHF. The presence of “renal-specific” non-traditional risk factors (Table 1) such as the effects of uraemia itself, renal anaemia, iron deficiency, carnitine deficiency, endothelial dysfunction and oxidative stressplay all play a role in cardiovascular disease progression. Emerging evidence also suggests that the complex interactions of disorders of renal bone disease seen in CKD (encompassing links between disturbances in vitamin D metabolism, hyperparathyroidism and in particular mineral disarrays such as the increases in serum phosphate) in conjunction with vascular calcification and arterial stiffness may represent important additional non-traditional risk factors in cardiovascular disease. However perhaps endothelial dysfunction plays a central role in the entire process of cardiovascular risk (10, 24).

In this article we review the array of potential factors involved in the cardio-renal interactions leading to an increased risk of heart failure, particularly focusing on current information on the effects of renal impairment and non-traditional risk factors on cardiac function. The renal insufficiency that occurs secondary to heart failure has been recently comprehensively reviewed and will only be mentioned briefly (24, 25). This review will also focus on aspects of biochemical and metabolic changes occurring in uraemic heart disease. A better understanding of the pathophysiology between the heart and the kidney is essential to formulate optimal management strategies and develop new strategies for future management of uraemic heart disease.

3. PATHOPHYSIOLOGY OF CARDIAC FAILURE

Anatomically and functionally, the kidneys have evolved to conserve extracellular fluid volume through retention of salt and water. The kidneys are ultimately responsible for the oedema seen in heart failure (26), and patients with heart failure tend to accumulate fluid before they develop overt oedema, due to the inability of the kidneys to excrete salt in a normal fashion (27). There is a continuous relationship between the level of kidney function and mortality rather than a threshold value below which reduced kidney function is a risk factor (28). Ronco et al have recently proposed a classification of cardio-renal/reno-cardiac disease (29). This classification has some merits but only type IV (chronic renal-cardiac disease - chronic kidney disease leading to the progression of chronic cardiac disease) is representative of the population described here and therefore the classification is perhaps of little clinical value (29).

Several homeostatic systems operate in the early stages of uraemic cardiac disease. The renin angiotensin
Table 2. Summary of the pathophysiological, biochemical and cellular actions and effects of aldosterone and angiotensin II in heart failure. (28, 29-39)

<table>
<thead>
<tr>
<th>Aldosterone</th>
<th>Angiotensin II</th>
</tr>
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<tbody>
<tr>
<td>Vascular remodelling</td>
<td>Vascular remodelling</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>Smooth muscle cell growth</td>
</tr>
<tr>
<td>Cardiac hypertrophy</td>
<td>Left ventricular cell hypertrophy</td>
</tr>
<tr>
<td>Inflammation and fibrosis</td>
<td>Interstitial fibrosis</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>Sodium and water retention</td>
</tr>
<tr>
<td>Arhythmogenesis</td>
<td>Vasopression secretion</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>Sympathetic nervous system activation</td>
</tr>
<tr>
<td>Baroreceptor dysfunction</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Sympathetic nervous system activation</td>
</tr>
</tbody>
</table>

Figure 1. Summary of the pathways involved in myocardial substrate metabolism. Glucose enters cells via the GLUT1 and GLUT4 insulin-dependent glucose transporters to form pyruvate (glycolysis) and ATP. Fatty acids enter cells via the FAT/CD36 transporters and are activated to acyl-CoA. Both pyruvate and fatty acids enter the mitochondria and undergo oxidation to produce acetyl-CoA for use in the Krebs cycle (TCA cycle) and nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2) for subsequent ATP production via the electron transport chain.

The aldosterone system (RAAS) plays a central role. Renin Angiotensin Aldosterone System activity progressively increases with disease activity in CHF (28, 30), with aldosterone II causing vasoconstriction (31). The magnitude and duration of reflex renal vasoconstriction are both exaggerated in CHF patients (32). Angiotensin II also promotes vascular remodeling, smooth muscle cell growth, interstitial cell dysfunction, sympathetic nervous system activation, vasopression secretion and stimulation of thirst (33), while subsequent aldosterone secretion (34) also causes vascular remodelling, cardiac hypertrophy, endothelial cell dysfunction, baroreceptor dysfunction, sodium and water retention, electrolyte disturbances, autonomic dysfunction, arrhythmogenesis and nephrosclerosis (35). Aldosterone is also involved in inflammatory and reparative processes, stimulating cytokine production, inflammatory-cell adhesion, chemotaxis, macrophage activation, fibroblast proliferation and synthesis of type I and II fibrillar collagens resulting in scar tissue formation and fibrosis (36-39) (Table 2). These changes are sensed by baroreceptors which modulate sympathetic neural outflow and vascular resistance to maintain homeostasis (40). A host of complex and interdependent neuro-hormonal pathways are thus activated to achieve haemodynamic stability within the circulatory system. Autonomic dysfunction is made worse by uremic toxins and amplification of the sympathetic activity by concurrent activation of the RAAS (41). This results in increased myocardial contractility, tachycardia, increased cardiac after-load due to vasoconstriction, increased cardiac preload due to venoconstriction, myocyte hypertrophy, increased risk of cardiac arrhythmias, sodium and water retention and accelerated progression of renal disease (42-44).

Normally cardiac tissue metabolizes free fatty acids (FFA) as its main energy source but this fatty acid oxidation (FAO) process requires more oxygen per adenosine tri-phosphate (ATP) produced in comparison to carbohydrate metabolism (45). In mild to moderate heart failure (HF) the myocardium still utilizes a significant amount of FFA as a substrate (46) in contrast to severe HF. At a cellular level there is a switch in energy provision from fatty acid oxidation to glucose metabolism, which increases plasma free fatty acids and increases oxygen wastage (Figure 1). This increase in plasma FFA is further exacerbated by nor-epinephrine, which further increases oxygen wastage by reduced glucose import into myocytes (47). Therefore one might anticipate an increase in FFA metabolism in heart failure but this is not always the case and the precise processes operating here remain unclear (46). However this increase in plasma FFA, in conjunction with the RAAS and catecholamines leads to activity of the sympathetic nervous system leading to myocardial insulin resistance (IR) (48). This insulin resistance may be a key step in the process of progressive cardiac dysfunction, from reduced glucose uptake by the heart in preference to FFA (49), but this remains a contentious theory (50). Experimental human and animal studies demonstrate evidence of energy starvation in heart failure reflected in a reduced phosphocreatinine:ATP ratio (51, 52), reduced contractility of individual myocytes (53), and altered calcium handling (54). Excess fatty acids may also be associated with uncoupled mitochondrial respiration (55). This is compounded by uraemia which accelerates the process and degree of insulin resistance. It also activates transcription factors such as peroxisome proliferators receptor-alpha (PPAR-alpha) (56), which in conjunction with reactive oxygen species (ROS) and lipid peroxidation products lead to an increase in uncoupling protein expression (55, 57). Finally with advancing uraemic heart failure PPAR-alpha is down regulated in addition to transcription factors that regulate mitochondrial biogenesis (PPAR-gamma co activator-1-alpha (PGC-1-alpha) (58, 59). This later transcription factor perhaps has a central role in altering the heart’s response to metabolic stress and a target for future therapy. The dynamics of this interaction maybe more complex due to the ubiquitous nature of these factors in many tissues.
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<table>
<thead>
<tr>
<th>Structural</th>
<th>Metabolic</th>
<th>Cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>remodelling of the heart – eccentric and concentric left ventricular hypertrophy</td>
<td>abnormal cardiac energetics with a switch to glucose metabolism</td>
<td>reduction of insulin mediated glucose uptake</td>
</tr>
<tr>
<td>reduced capillary density with alterations in myocyte number</td>
<td>energy starvation</td>
<td>Changes in GSK-3-beta/AKt/PIP3K signalling</td>
</tr>
<tr>
<td>myocardial fibrosis</td>
<td>Reduced phosphocreatine/ATP ratio</td>
<td>calcium cycling with abnormal control of intracellular calcium handling in cardiomycocyte</td>
</tr>
<tr>
<td>coronary microvascular &amp; macrovascular disease</td>
<td>reduced stability of energy rich nucleotides</td>
<td>altered activity of GLUT 4</td>
</tr>
</tbody>
</table>

Table 3. Summary of the structural, metabolic and cellular changes occurring in the uraemia heart

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Cellular</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Autoantibodies</td>
</tr>
<tr>
<td></td>
<td>Endothelial damage</td>
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<td></td>
<td>Endothelial injury</td>
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<tr>
<td></td>
<td>Glomerulosclerosis</td>
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<tr>
<td></td>
<td>Myocyte damage</td>
</tr>
<tr>
<td></td>
<td>Myocardial fibrosis</td>
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<tr>
<td></td>
<td>Reduced cardiac output</td>
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<td></td>
<td>Uraemic cardiac disease</td>
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</tbody>
</table>

Table 4. Summary of the main middle molecules currently identified as being present in uraemia with biological potential

- Adrenomedullin
- AGE
- Angiogenin
- Advanced oxidation protein products (AOPP)
- Atrial natriuretic peptide
- Cholecystokinin
- Clara cell protein
- Complement factor D
- Cytokines
- Delta sleep inducing protein
- Endothelin
- beta-Endorphin
- Fibroblast Growth Factor-23 (FGF-23)
- Ghrelin
- Glomerulopressin
- GIP
- GIP II
- Homocysteine
- Methionine-enkephalin
- Beta-2-Microglobulin
- Neuropeptide Y
- Orexin A
- Oxalic acid
- Oxidised LDL
- IG Light Chains
- Retinol binding protein

4. WHAT FACTORS ARE IMPLICATED IN URAEMIC CARDIAC DISEASE?

The uraemic heart has a specific phenotype due to a series of complex changes at structural, metabolic and cellular levels (Table 3) leading to functional effects on myocyte contractile function, reduced cardiac output and cardiac failure. Several mechanisms operate in uraemia to exacerbate these changes. Uraemia leads to the production of a large number of “toxins” or middle molecules with biological potential (Table 4). Many constituents of this abnormal milieu may lead to the adverse cardiac profile through a number of vaso-active, pro-inflammatory and pro-fibrotic pathways detailed below.

4.1. Oxidative stress

Increased oxidative stress, an imbalance between ROS production and degradation (i.e. an uncoupling of nitric oxide production), is seen in the early stages of renal disease and forms part of the mechanism responsible for endothelial damage (60, 61). It is a risk factor for developing CHF through impairment of the cardiac microcirculation (endothelial dysfunction). ROS are produced during mitochondrial related energy production (62). Excessive production causes cellular and tissue damage by interacting with bio-molecules such as lipids and proteins leading to alterations in structure and function. These then favour atherosclerotic processes culminating in direct cytotoxicity of both renal and cardiac cells (63, 64). Uraemic toxins lead to an increase in circulating asymmetric dimethylarginine ((ADMA) - an endogenous inhibitor of nitric oxide synthase (NOS)) thus reducing the bioavailability of nitric oxide (NO) (65). Many factors (L-NAM, calcium, and oxygen and gene activation) influence the activity of NOS, a key component of ROS function, in particular AMDA accumulation in CKD which leads to endothelial injury (66, 67) (Figure 2). Within the kidney, NO antagonises angiotensin II at the glomerular and proximal renal tubule level (68, 69) and inhibits smooth muscle (70) and mesangial cell growth (71). Mechanisms include a blunting of the NOS activity in heart failure (72) and an impairment of NO release to various stimuli such as exercise in CHF (73). Patients with renal dysfunction exhibit abnormal arterial endothelial function (74). In uraemia an analogue of L-arginine accumulates and inhibits NO production (75) with its subsequent detrimental role of further promoting hypertension and vasoconstriction with increases in afterload, hypertension and renal dysfunction (76). CKD appears to be a primary cause of endothelial dysfunction. Factors such as hyperglycaemia lead to an overproduction of superoxide by the mitochondrial electron transport chain increasing expression of Nicotinamide adenine dinucleotide phosphate (NADPH) and inducible NOS activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa-B) (77). Interestingly blockade of the renin-angiotensin system with an angiotensin converting enzyme inhibitor (ACEi) and use of calcium channel blockers both leads to a reduction in markers of oxidative stress and circulating dimethylarginine (67).

4.2. Inflammation

CKD also creates a persistent low grade inflammatory state, with activation of cytokines such as C-reactive protein (CRP), interleukin 6 (IL-6), pentraxin-3, tumor necrosis factor alpha (TNF-alpha), adhesion molecules and fibrinogen, (78-80). These changes reflect both reduced renal clearance and increased production, and are independent predictors of cardiovascular outcome in CKD patients (81-83). This state of chronic inflammation induced by the persistent uraemic milieu may modulate existing cardiovascular risk factors via triggering endothelial dysfunction and exacerbating the atherosclerotic process. The end result is both cardiac and renal injury from destruction of cells and tissues. Both oxidative stress and inflammation processes overlap to cause clinical changes including vascular calcification (84).
The inflammatory state also leads to other effects such as decreased iron absorption, increased hepcidin and erythropoietin resistance which contribute to the anaemia seen in uraemia (85).

4.3. Vitamin D deficiency and calcium phosphate metabolism

Chronic kidney disease is associated with abnormal calcium-phosphate metabolism, which leads to accelerated medial calcification of coronary blood vessels and cardiac valves (86, 87). The increased arterial stiffness that occurs in CKD with decreased elasticity contributes to cardiac afterload and left ventricular hypertrophy (LVH) and stiffness and diastolic dysfunction (88-90). Elevated serum calcium and phosphate levels are risk factors for CHF in dialysis patients (91). There is also a direct link between hyperphosphataemia and mortality in patients with chronic renal failure (91). Several studies have recognized other factors that contribute to vascular calcification including diabetes, inflammation and time on dialysis (92, 93). The mechanism leading to myocardial dysfunction in hyperparathyroidism is purported to be uncoupling oxidative phosphorylation, reducing cellular ATP concentrations and impairing calcium extrusion leading to calcium overload in cardiomyocytes, initiated by activation of parathyroid hormone (PTH) receptors on myocytes (94).

Vitamin D deficiency (reduced circulating 1, 25 \((\text{OH})_2\) vitamin D3 (active Vitamin D) due to reduced 1-hydroxylase activity in the kidney as renal function declines), which is common in CKD, also appears important in relation to possible left ventricular remodeling.
and vascular calcification (95). A degree of nutritional Vitamin D deficiency also occurs in CKD ((25 (OH) vitamin D) and may also be involved in the process of accelerated cardiac risk. Vitamin D3 plays a role in the maintenance of cardiac cell contraction, proliferation, hypertrophy and protein and collagen expression, and also affects vascular tone. This is in part explained by the calcium uptake by cardiac myocytes being regulated by vitamin D3 (96). Thus a deficiency may lead to LVH via impairment of contractile function, increasing collagen deposition and effects on the RAAS (97). Furthermore, the activation of PTH leads to vascular smooth muscle cell (endothelial cell) calcification and LVH from increased calcium phosphate product (98).

Fibroblast growth factor-23 (FGF-23) inhibits 1-hydroxylation, potentially aggravating vitamin D deficiency and leading to hyperparathyroidism and serving as a risk factor or biomarker for cardiac disease. This novel protein closely interacts with the transmembrane protein klotho and both may serve as useful biomarkers associated with cardiovascular disease. Mirza et al have shown that FGF-23, which increases with CKD progression, is associated with LVH and a marker and/or potentially an aetiological cofactor involved in the progression of cardiac disease (99). Recent studies using vitamin D analogues demonstrate improved survival on haemodialysis (100-103). They have also shown a reduction in cytokine production (TNF-alpha, increased IL-10) and LVH from increased heart failure mass (104). Finally, early data suggests that vitamin D therapy may reduce insulin resistance (105).

4.4. Carnitine deficiency
Carnitine, a key metabolite in cellular metabolism is significantly depleted from the myocardium during ischemia (106). Carnitine plays a pivotal role in myocardial energy metabolism, as the transporter of long chain fatty acyl intermediates across the inner mitochondrial membrane for beta oxidation (107) and as a key regulator of carbohydrate metabolism by modulation of the intra-mitochondrial acetyl-CoA/CoA ratio (108). Secondary carnitine deficiency is a frequent observation in uremic patients, particularly in maintenance haemodialysis therapy (109). Thus the presence of carnitine deficiency in uraemia may further aggravate the deleterious myocardial metabolic remodeling during ischemia, and exacerbate contractile dysfunction. Experimental and clinical studies have reported beneficial effects of carnitine treatment in the setting of non-uraemic myocardial ischemia and reperfusion including, modulation of myocardial metabolism (45, 110), reduction in necrotic cell death and infarct size (111), decrease in the incidence of arrhythmias (112) and preservation of mechanical function (113). Clinically, carnitine replacement appears to improve exercise performance, muscle weakness, fatigue and cramps in addition to benefits on cardiac function (114). More recent studies suggest carnitine supplementation may limit development of myocardial hypertrophy and myocyte injury during ischemia in uraemic animals. There is a reduction in infarct size in reperfused isolated rat hearts treated with acute L-carnitine and a decreased release of myocardial creatinine kinase in patients with acute myocardial infarction (111, 113)

4.5. Anaemia and iron deficiency
The prevalence of anaemia in patients with CHF and CKD is high, with only 29% of patients having a haemoglobin level above 11g/dL. (115, 116). The main causes are erythropoietin deficiency, functional iron deficiency and the anaemia of chronic disease (117, 118).

Anaemia is a risk factor for LVH, heart failure and all-cause mortality in the ESRD population (119). Chronic anaemia results in insufficient oxygen delivery to tissues and increased cardiac work with subsequent ventricular remodeling and cardiac dysfunction (120). This results in increased sympathetic activity leading to further oxygen requirements and potential ischemia. Correction of anaemia with recombinant erythropoietin in patients with renal dysfunction has beneficial effects, including the regression of LVH, and reduction in hospitalizations (121, 122). In patients with CHF, correction of anaemia increases the ejection fraction, improves prognosis and can reduce hospitalizations but also led to exacerbations of CHF (123).

At a cellular level in uraemia erythropoietin abrogates the increased oxygen consumption and reduced cardiac efficiency seen in erythropoietin naive uraemic rats. There is a reduction in palmitate oxidative metabolism in favour of increased glucose utilization (re-expression of the fetal phenotype) and alterations in myocyte contraction and relaxation. Recombinant erythropoietin may reduce myocyte apoptosis and enhance cardiac fibrosis via phosphotyrosylinsitol 3-kinase/protein kinase B (PI3K/Akt) and janus kinase-2/signal transducer and activator of transcription-5 (JAK2/STAT5) pathways by downstream effects on glycogen synthase kinase-3-beta (GSK-3-beta) acting to block mitochondrial permeability pore opening. It may also be cardio-protective from acting via protein kinase-C (PKC) to increase the opening of mitochondrial K ATP channels (124-125). Erythropoietin has also been shown to modulate NO via up-regulation of endothelial nitric oxide synthase (eNOS). This up-regulation occurs via activation of the PI3K-Akt pathway (126-129). The result is a reduction in oxidative stress and cellular damage (130, 131) (Figure 3).

Recent studies reassessing erythropoietin derivatives and iron in anaemic patients with heart failure demonstrate varied results (132). Partial correction of anaemia among dialysis patients has been shown to reduce left ventricular mass, but the effects of increasing haemoglobin on cardiovascular events in pre-dialysis patients are somewhat controversial as to the level of anaemia correction to provide benefit rather than detriment (133-136). This may relate to correction in platelet dysfunction and increased blood viscosity. The importance of iron deficiency in the genesis of uraemic cardiomyopathy remains unclear. The limited ATP production in iron deficient mitochondria can contribute per se to cardiac hypertrophy due to changing balance between ATP supply and demand. Furthermore, studies on mitochondria of cardiac as well as skeletal muscle have demonstrated substantial alterations in the process of
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Figure 3. Schematic representation of the potential signalling pathway of Erythropoietin (EPO) mediated through its specific cellular receptor - EPO receptors. Once bound, EPO causes phosphorylation and subsequent activation of the receptor-associated Janus Kinase2 (JAK2) and activation of signalling cascades of proteins including STAT 5 (signal transducer and activator of transcription 5). This leads to transcriptional activation of NF-kappa-B-dependent mitogenic and anti-apoptotic Activation of the erythropoietin receptor also stimulates the phosphatidylinositol 3-kinase (PI3K) pathway which has down stream effects on pro-survival pathways including Akt, protein kinase C (PKC), glycogen synthase kinase 3-beta (GSK-3b) and nitric oxide (NO) with eventual effects on the mitochondrial pore opening (mPTP) and apoptosis. mKATP = mitochondrial ATP sensitive potassium channel. ROS= reactive oxygen species (124-13).

oxidative phosphorylation in iron deficient rats (137, 138). A further important factor in CKD and iron deficiency and cardiac disease is the increased inflammation which is present. This leads to increased hepcidin thus affecting the utilization of iron by cells such as the mitochondria (85, 139-141).

4.6 Proteinuria and albuminuria

An initial insult to the kidneys results in a loss of nephrons leading to changes in renal haemodynamics (142). Adaptive changes in the form of glomerular hypertension increase the filtration capacity of the remaining nephrons, which ultimately becomes detrimental (143). Increased glomerular capillary pressure (142, 143) enlarges the radius of the pores in the glomerular membrane leading to increased protein content within the glomerular filtrate, which in turn increases the endocytosis of protein by tubular epithelial cells resulting in a nephritogenic effect. Microalbuminuria in the absence of clinical proteinuria is caused by endothelial dysfunction. (144, 145), decreased glomerular charge selectivity, size selectivity and increased intraglomerular pressures (146). Prevalence of microalbuminuria is a predictor of cardiovascular risk and CHF (147, 148). Abnormal accumulation of proteins activates genes encoding vaso-active and inflammatory substances such as endothelin, chemokines and cytokines, resulting in fibrogenesis and renal scarring (149). Mesangial cells have properties similar to vascular smooth muscle cells (VSMC) and therefore factors affecting vascular smooth muscle cells...
will therefore have a bearing on the function of these mesangial cells. Pathological mechanisms in the kidney, partly mediated by angiotensin II, include effects on the contractile properties of the mesangial cells, which in turn dictate glomerular size and filtration area, raises glomerular capillary hydraulic pressures and the plasma concentrations of macromolecules within the glomerular capillary tuft, and has independent effects on sieving function by modifying the F-actin fibre assembly of the podocytes and modulating the matrix network and collagen content of the glomerular basement membrane (143, 150, 151).

The reasons for the poor cardiac outcomes in the presence of proteinuria are multi-factorial. Low serum albumin causes structural and functional abnormalities in the myocardial contractile proteins, actinomysin and its precursor proteins and is accompanied by an increase in capillary permeability and an attenuated endothelium-dependent response to vasodilator stimuli (152) and local microvascular structural and functional changes resulting in an increase in peripheral vascular resistance and subsequent increase in cardiac afterload. Albuminuria is also associated with other well-established risk factors for the development of CHF such as hyperglycaemia, hypertension, smoking, and dyslipidaemia (153-155). In primary hypertension, it is also associated with factors that increase cardiovascular risk, such as endothelial dysfunction, insulin resistance, hyperlipidaemia, and a high body mass index (156). Microalbuminuria is also associated with abnormal left ventricular geometry, lower left ventricular contractility and abnormal diastolic flow patterns independent of systolic blood pressure, age and diabetes mellitus suggesting parallel cardiac and microvascular damage possibly due to the role of angiotensin II as a growth factor involved in LVH and renal vascular changes (148, 151). There is growing evidence that reduction and normalisation of proteinuria is a key treatment goal for renal protection and possibly cardio-protection (157-159).

4.7. Homocysteine and Hyperuricaemia

Small reductions in GFR are associated with an increase in total plasma homocysteine due to impaired extra-renal metabolism (160). Indeed more than 90% of patients with advanced CKD have hyperhomocysteinaemia. Prospective observational studies show a greater risk of coronary artery disease in the presence of elevated homocysteine levels (161) and it is an independent risk factor for the development of cardiovascular disease (162). Mechanisms include inducing dysfunction of the vascular endothelium, (163) increasing proliferation of VSMC (164) and increasing oxidative stress (165). Interestingly data from the “HOST” multi-centre double blind clinical trial in patients with renal disease with high homocysteine levels with intervention with folate, pyridoxine and cyanocobalamin versus placebo have not demonstrated any clinical benefit despite a mean reduction in homocysteine of 6.2 micromol/L (166). A more recent randomized study verified this finding in haemodialysis patients (167). This may be due to the lack of normalization of homocysteine levels with treatment despite the significant reduction or the multiple other risk factors present having a greater effect.

Hyperuricaemia, which is often present in renal dysfunction, correlates with the existence of nephrosclerosis (168). Higher levels appear predict increased mortality in patients with chronic heart failure, but the mechanism is unclear (169).

4.8. Lipids

There is a wide spectrum of changes in lipoproteins in uremia which tend to be qualitative rather than quantitative and vary depending on the severity of renal disease. Adverse effects on lipid profiles in renal impairment include reduced high density lipoprotein (HDL) levels, probably due to decreased levels of apo A-1, and apolipoprotein which is a necessary constituent of HDL (170) and an increase in low density lipoprotein (LDL) cholesterol (171). Prolonged lower levels of HDL are associated with a 20% higher risk of coronary artery disease (172). Apolipoprotein B is increased; there is hypertriglyceridaemia and elevated levels of oxidised LDL activity (173-175). The latter is perhaps due to inadequate removal rather than excess production (174-175). Lipoprotein(a) is a prominent and independent risk factor in atherogenesis in dialysis patients (176) and levels are elevated in renal failure and are associated with a 1.7-fold higher risk of coronary-artery disease (177). However, in severe CKD the pattern of dyslipidaemia is unique and there is a ‘U-shaped’, rather than linear, relationship between cholesterol and mortality (174, 178). This might relate to the presence of inflammation leading hypercholesterolaemia which may affect acute mortality thus complicating the risk. Interventions to reduce cholesterol in haemodialysis patients have shown that despite improvements in LDL cholesterol by 24% there was no significant improvement in cardiovascular outcomes (179, 180), although they still appear effective in mild to moderate CKD (181).

4.9 Left ventricular hypertrophy (LVH) and metabolic changes

Chronic kidney disease is associated with several adverse alterations in cardiac structure. Left ventricular hypertrophy is particularly prevalent in CKD patients. The incidence of LVH is inversely related to renal function, ranging from 26% in patients with a GFR greater than 50mls/min to 75% in patients starting renal replacement therapy (182-184). The presence of LVH in renal failure is an independent predictor of cardiac symptoms and ESRD. LVH begins early in the course of renal failure - the pathogenesis of LVH includes haemodynamic factors such as blood pressure, volume load, arterial structure and blood viscosity, and non-haemodynamic factors such as activation of the sympathetic nervous system and the RAAS, genetic factors, age, sex, race, salt intake, obesity and alcohol. Additional contributing factors specific to renal dysfunction include anaemia, fluid overload, and arterial stiffness and vascular calcification (183). The underlying features that distinguish pathological from physiological hypertrophy, and which leads to the progression from compensated to decompensated pathological hypertrophy are incompletely understood. The geometry of the LVH is important, with concentric patterns (classic wall thickening with a reduction in the ventricular
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Figure 4. Types of cardiac hypertrophy: Physiological hypertrophy is characterised by a reversible, uniform hypertrophy in which muscle wall and chamber enlarge together without cardiac dysfunction. Pathological hypertrophy can be either concentric (thickening of chamber wall with reduction in chamber size) or eccentric (dilation of ventricular chamber). Function is impaired and fibrosis present. It is not (or only partially) reversible. DCM - dilated cardiomyopathy; LV - left ventricle; RV - right ventricle. (modified from Heineke, & Molkentin 185)

Both these forms of LVH occur in uraemia. The hypertrophy of the cardiac smooth muscle cells is mediated by angiotensin II (186). Sustained increases in ventricular mass create an imbalance of the growth of the myocardium and coronary capillaries, (reduced myocyte capillary density), observed in both experimental and human uraemia (187-188) leading to reduced blood flow to the hypertrophied myocardium. This is associated with ischaemia and cardiac dysrhythmias due to disturbed repolarization, and progresses to cardiac dysfunction and heart failure from both diastolic and systolic dysfunction (57) and subsequent poor clinical outcomes (189, 190).

Underpinning the biochemical and molecular changes that lead to heart failure is a complex system of intracellular signaling pathways. Unraveling this network is vital to determining the mechanisms involved in the progression from hypertrophy to failure, and may identify novel therapeutic targets in the future.

4.10. Insulin resistance and glycaemic control

Insulin resistance is a common feature in a number of conditions which result in an increased risk of cardiovascular disease, including cardiac hypertrophy, CKD and heart failure (195-198). Hypertension is also closely associated with insulin resistance, renal failure and heart failure (199). Previous studies on experimental models of insulin resistance have demonstrated increased
Table 5. Summary of the proteins and processes involved pro-survival and pro-death pathways involved in signalling in uraemic heart disease

<table>
<thead>
<tr>
<th>Pro-survival</th>
<th>Pro-death triggering apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK-STAT signalling</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>PIP3K - Akt signalling</td>
<td>Sympathetic stimulation</td>
</tr>
<tr>
<td>Inhibition of cyclophilin D</td>
<td>Increased cytosolic calcium</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Akt-PIP3K pathways for insulin signalling. Insulin resistance decreases phosphorylation of Akt (protein kinase B) and subsequently phosphorylation of GSK-3β (glycogen synthase kinase 3-beta). PKA = protein kinase A and PKC= protein kinase C

myocardial utilization of fatty acids and decreased glucose oxidation, accompanied by a reduction in cardiac efficiency (200, 201). Thus in uraemia insulin resistance may exacerbate metabolic remodeling in the heart by limiting the uptake and metabolism of glucose, predisposing the uraemic heart to progress into chronic energy deficiency and later failure. Insulin resistance in renal disease results in endothelial dysfunction and increased sodium reabsorption, which then contribute towards the progression of CHF. However it is not clear how insulin resistance, uraemia and heart failure interrelate to produce the cardiac morbidity seen in renal disease. It may be the close association of insulin resistance with atherosclerosis and cardiovascular mortality in the general population is critical, and indeed it has been shown to be an independent predictor of cardiovascular mortality in patients with end stage renal disease (198). The signaling pathways of insulin resistance in uraemic heart disease are complex and undefined but recent data has given some insight into the effects of uraemia on downstream signaling targets including Akt/ PKC (202, Figure 5). Glucose transport via GLUT4 appears to remain intact but there may be changes in post translational modification as a result of uraemia leading to effects on insulin resistance (203). Preliminary data from our lab suggests no or little change in Akt/GSK-3-beta but examination of isoforms is ongoing (204). In the failing uraemic heart there is an imbalance between signaling pathways promoting cell survival and cell death (Table 5) with a final common result of reduced myocyte numbers. Uraemic cardiomyopathy may also cause reduction in the expression of the nuclear receptor PPAR-alpha and its co-activator PGC-1-alpha, which have been identified as the master switches for the myocardial metabolic remodeling (202, 205)

In summary an understanding of links between cardio-renal disease is essential. The previous sections have highlighted the array of risk factors critical in the pathogenesis of uraemic cardiac disease. The literature demonstrates that renal specific and other factors are important and potentially modifiable. Emerging novel areas including vitamin D deficiency and phosphate balance and metabolic adaptations are growing in importance. The links between inflammation, endothelial dysfunction, oxidative stress and cardiac disease still remain somewhat obscure. In formulating a potential unifying pathway of cardiac risk in the development of uraemic cardiac disease, one might consider the process of endothelial dysfunction induced by a number of micro and macro mechanisms with changes in metabolic profile and the presence of insulin resistance playing critical roles in the genesis of cardiac disease in the presence of CKD (206).

5. TREATMENT OPTIONS FOR URAEMIC HEART DISEASE

5.1. Established treatments

Current therapies largely consist of those used in patients with CHF and normal renal function translated into a population of CKD patients. Diuretics remain the standard treatment of acute cardiac failure. However they promote insulin resistance, so in the longer term may adversely affect myocardial metabolism and exacerbate the energy starvation experienced by the failing heart (207). Digoxin now demonstrates a consistent fall in hospitalizations when used in patients with CHF and sinus rhythm (208). The role of beta blockers in particular those with combined alpha, beta activity which appear to reduce FFA extraction is now well established in CHF to lead to a decreased morbidity and mortality (209-212). Their role and benefits in patients with CKD is less well defined.

Modern therapy with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) have improved quality of life and decreased hospital admissions. Numerous large randomized trials have shown the benefits of ACEi on mortality, morbidity and exercise capacity in all degrees of heart failure even after ischaemic events (213-218). ACEi improve vascular endothelial function, enhancing fibrinolysis, antagonizing the proliferation of vascular smooth-muscle cells and rupture of plaques (219, 220). Decreased breakdown of bradykinin which releases NO is one mechanism by which endothelial function is improved (221). The combined effects of ACEi therapy which reduces thirst and proximal tubular re-absorption of sodium and interaction with the hydro-osmotic effect of vasopressin helps to offset the physiological factors causing impaired excretion of water. ACEi also decrease the markedly elevated left ventricular wall stress of patients
with congestive heart failure that may lead to progressive cardiac dilatation and death (222, 223). Some reversal of left ventricular hypertrophy and remodeling also occurs (224-226). ARB’s are also promising in CHF. This is perhaps through their haemodynamics, anti-inflammation, endothelial function from a reduction in mRNA and protein expression of endothelin, and TGF-beta dependent inhibition of fibrosis (227). The RALES and Eplerenone studies (228, 229) have confirmed the benefits of aldosterone antagonists via improvements in cardiac performance due to a reduction in systemic vascular resistance, vasodilatation secondary to decreases in interstitial oedema and a subsequent decrease in cardiac afterload (228-230).

The Choice study demonstrated a paradoxical inverse relationship between serum cholesterol and mortality in dialysis patients (231). Perhaps statins may help reduce cardiac damage by increasing eNOS activation which increases NO from L-arginine via activation directly through the PI3K/Akt pathway and indirectly through Rho activation. Thus interfering with this pathway of damage in early CKD may reduce inflammatory markers and oxidative stress (232). However once ESRD is established the benefits of statins are much less clear in relation to cardiovascular protection (179, 180). Despite early studies suggesting some benefit from the pleotropic effects of statins via affects on oxidized LDL (233) current data is disappointing. These negative results from two major studies may perhaps be explained by the persistent high triglyceride levels or the increase in small dense LDL particles seen in severe CKD or from presence of a mixed array of interacting risk factors in severe renal disease. The ongoing study of heart and renal protection (SHARP) which have approximately 9000 patients with a composite end point of cardiac disease, non fatal and fatal stroke may provide further insight (234).

Several mechanical advances can improve cardiac function. Cardiac resynchronization with implantable pacemakers improves glucose metabolism and reduces insulin resistance. It also improves myocyte cell survival mediated by the Akt-BAD (BeL2 antagonist of cell death) signaling pathway. Implantable cardioverter defibrillators improve mortality while left ventricular assist devices may improve calcium cycling and adrenergic responses thus augmenting cardiac function (203, 235).

5.2. Other treatments in heart failure and their effect on renal function

Studies on humans have demonstrated that the administration of oral vasopressin antagonists to patients with CHF significantly increased urine flow, plasma sodium whilst reducing urine osmolality, confirming an increase in solute-free water clearance. They behave as ‘aquaretics’ causing loss of water alone with no effect on electrolyte excretion. Studies using combined V1 and V2 receptor antagonists (236) and selective V2 receptor antagonists (237) have been reported with favourable short-term results.

Exogenous recombinant human brain natriuretic peptide (BNP), nesiritide, has been demonstrated to produce a rapid and sustained beneficial haemodynamic effect when given intravenously for symptomatic decompensated HF patients (238-240). These beneficial effects produce a moderate increase in urine output during nesiritide infusions (240). In a canine model with CHF, repeated short-term administration of subcutaneous BNP resulted in an improvement in cardiovascular haemodynamics (241) that may be used for chronic administration in humans. Synthetic BNP had beneficial haemodynamic and renal effects when used intravenously in experimental heart failure. In the presence of uraemia the effects are unknown (242).

Natriuretic peptides are catabolized by neural endopeptidases. Inhibition of this breakdown step could lead to potentiation of the beneficial circulatory and renal effects observed with the natriuretic peptides. Vasopeptidase inhibitors are molecules which simultaneously inhibit neutral endopeptidase and ACE (243-244). Vasopeptidase inhibitors have broad potential benefit in renal disease as well as in hypertension and heart failure (245).

Gottlieb et al (246) using an A1 adenosine receptor antagonist in patients with heart failure on standard treatment concluded that the antagonist conferred a protective role against the commonly observed decline in GFR associated with loop diuretics. An increase in urine output was also demonstrated. The endothelin receptor antagonist BQ-123 increased survival in rats with heart failure (247). Administration of antibodies to tumor necrosis factor improved cardiac function in patients with sepsis (248). The effects on the kidney of these treatment modalities are not known.

5.3. Renal specific therapies

Anaemia correction in CKD and heart failure with iron and erythropoietin therapy improves quality and heart failure parameters (115, 119, 122, 123, 132). Normalisation of haemoglobin is not recommended but conservative improvement to a haemoglobin target of 12g/dL seems optimal (135). A recent study has shown benefit of intravenous iron therapy in in heart failure and iron deficiency (249). Longer term studies are necessary to examine for possible adverse effects of excess labile iron leading to oxidative stress and potentially influencing both cardiac and mitochondrial function (250).

Vascular calcification is multi-factorial in CKD and potentially mediated by many stimuli including mineral changes and use of interventions such as phosphate binders and vitamin D therapy. Currently mainly epidemiological evidence indicates that treatment of mineral bone disease from a cardiovascular perspective may be beneficial. Calcium based phosphates binders may lead to increased progression of vascular calcification and arterial stiffness and possible use of the non calcium based binders may be useful in limiting cardiac disease progression in CKD (251). Further randomised controlled studies are required to confirm whether modulation of vitamin D and the calcium
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sensing receptors with calcimimetics and active vitamin D analogues is of clinical value.

The option of mechanical ultrafiltration in unstable acute heart failure has been recommended as an appropriate therapeutic alternative not only to improve extracellular volume overload, but also to mitigate neurohumoral stimulation (252). In 1949 Schneier son first introduced intermittent peritoneal dialysis for severe cardiomyopathy refractory to conventional treatment (253). Since that landmark paper several groups have reported use of ultrafiltration and/or peritoneal dialysis for the effective treatment of severe heart failure (254, 255) and to remove excessive salt and water in patients (256-261). This is a current revived area of intervention.

5.4. Other future targets - The metabolic pathways to reduce uraemic heart disease

There is great interest in correcting the metabolic changes to a heart which is ‘running out of fuel’ (262) and therefore energy deficient as the heart normally needs to manufacture more than 70 times its own weight in ATP daily (263). A recent review has summarized potential targets which may be adopted but in uraemia this may not be so simple (235). Manipulation of various parts of the signaling pathway of the RISK pathway (Reperfusion injury salvage kinase pathway of pro-survival proteins; Table 5) in uraemia may prove a useful intervention to protect the heart especially during the repetitive ischaemic reperfusion injury seen in haemodialysis patients (264).

Recent data from our lab suggests, that the insulin mediated protective which is lost in the uraemic population may be partly restored using insulin sensitizers (PPAR-gamma agonists) such as rosiglitazone and pioglitazone (unpublished data). These PPAR-gamma agonists seem promising with their multiple actions including anti-inflammatory, antihypertensive, anti-proteinuric, and insulin sensitizing (265). Recent clinical data is however conflicting especially in relation to their effects on fluid and sodium retention (266). A recent review has summarized potential targets which may be adopted but in uraemia this may not be so simple (235). Manipulation of various parts of the signaling pathway of the RISK pathway (Reperfusion injury salvage kinase pathway of pro-survival proteins; Table 5) in uraemia may prove a useful intervention to protect the heart especially during the repetitive ischaemic reperfusion injury seen in haemodialysis patients (264). Recent data from our lab suggests, that the insulin mediated protective which is lost in the uraemic population may be partly restored using insulin sensitizers (PPAR-gamma agonists) such as rosiglitazone and pioglitazone (unpublished data). These PPAR-gamma agonists seem promising with their multiple actions including anti-inflammatory, antihypertensive, anti-proteinuric, and insulin sensitizing (265). Recent clinical data is however conflicting especially in relation to their effects on fluid and sodium retention (266). A recent review has summarized potential targets which may be adopted but in uraemia this may not be so simple (235). Manipulation of various parts of the signaling pathway of the RISK pathway (Reperfusion injury salvage kinase pathway of pro-survival proteins; Table 5) in uraemia may prove a useful intervention to protect the heart especially during the repetitive ischaemic reperfusion injury seen in haemodialysis patients (264).

Finally in heart failure accumulation of fatty acyl compounds, due to the reduced uptake of lipids results in sequestration of coenzyme A. The end result is an inhibition of the key catalytic enzyme pyruvate dehydrogenase. This leads to reduced fatty acid and glucose utilisation from the Krebs cycle and energy starvation and lipotoxicity. Stimulating glucose utilization with drugs such as ranolazine and trimetazidine may abrogate this and improve cardiac function via a reduction in fatty acid oxidation (235, 274). A more recent drug perhexilene, a carnitine palmitoyl transferase-1 inhibitor (a mitochondrial FFA transport blocker) has also shown early promise. Other targets in the metabolic pathway are currently under study (235).

6. PERSPECTIVE

Whether it be from a prognostic, pathophysiological, metabolic or therapeutic aspect, it is clear that the intricate relationship present between the heart and the kidney is difficult to unravel and separate. Renal dysfunction plays a key role in addition to non-traditional factors in uraemic heart failure which will need considering in future therapies. Nephro-cardiology may well be an important concept in the future (275).

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**Send correspondence to:** Sunil Bhandari, Department of Renal Medicine, Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, Kingston Upon Hull, United Kingdom. Tel: 44-1482674566, Fax: 44-1482674998, E-mail: sunil.bhandari@hey.nhs.uk

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