[Frontiers in Bioscience 16, 1364-1387, January 1, 2011]

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

TABLE OF CONTENTS

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 compex 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

Table 1. Summary of classical, renal specific and other risk factors in uraemia for cardiovascular disease and heart failure (45, 203)

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

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 stressmay 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 reno-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)

Aldosterone	Angiotensin II
Vascular remodelling	Vascular remodelling
Nephrosclerosis	Smooth muscle cell growth
Cardiac hypertrophy	Left ventricular cell hypertrophy
Inflammation and fibrosis	Interstitial fibrosis
Endothelial dysfunction	
Sodium and water retention	Vasopression secretion
Arrythmogenesis	Stimulation of thirst
Electrolyte disturbances	
Baroreceptor dysfunction	Vasoconstriction
Autonomic dysfunction	Sympathetic nervous system activation

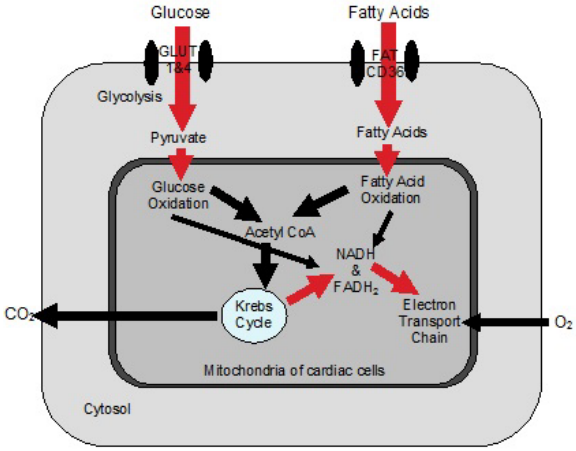

Figure 1. Summary of the pathways involved in myocardial substrate metabolism. Glucose enters cells via the GLUT1 and GLUT4 insulin-dependent glucose transporters to form pyruvate (glyocolysis) and ATP. Fatty acids enter cells via the FAT/CD36 transporters and are activated to acyl-CoA. Both pyruvate and fatty acids enter the mitochondria and undergo oxidation to produce aceyl 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.

aldosterone system (RAAS) plays a central role. Renin Angiotensin Aldosterone System activity progressively increases with disease activity in CHF (28, 30), with angiotensin 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 fibrosis, sympathetic nervous system activation, vasopressin 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, arrythmogenesis 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 uraemic 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 pre-load due to venoconstriction, myoctye 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.

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

Structural	Metabolic	Cellular
remodelling of the heart – eccentric and concentric left ventricular hypertrophy	abnormal cardiac energetics with a switch to glucose metabolism	reduction of insulin mediated glucose uptake
reduced capillary density with alterations in myocyte number	energy starvation	Changes in GSK-3-beta/AKt/PIP3K signalling
myocardial fibrosis	Reduced phosphocreatine/ATP ratio	calcium cycling with abnormal control of intracellular calcium handling in cardiomyocyte
coronary microvascular & macrovascular disease	reduced stability of energy rich nucleotides	altered activity of GLUT 4

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
Cholecystokin
Clara cell protein
Complement factor D
Cystatin C
Cytokines
Delta sleep inducing protein
Endothelin
beta-Endorphin
Fibroblast Growth Factor-23 (FGF-23)
Ghrelin
Glomerulopressin
GIP I
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 myoctye 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 bioavalability of nitric oxide (NO) (65). Many factors (L-NAMA, 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 fibringogen, (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).

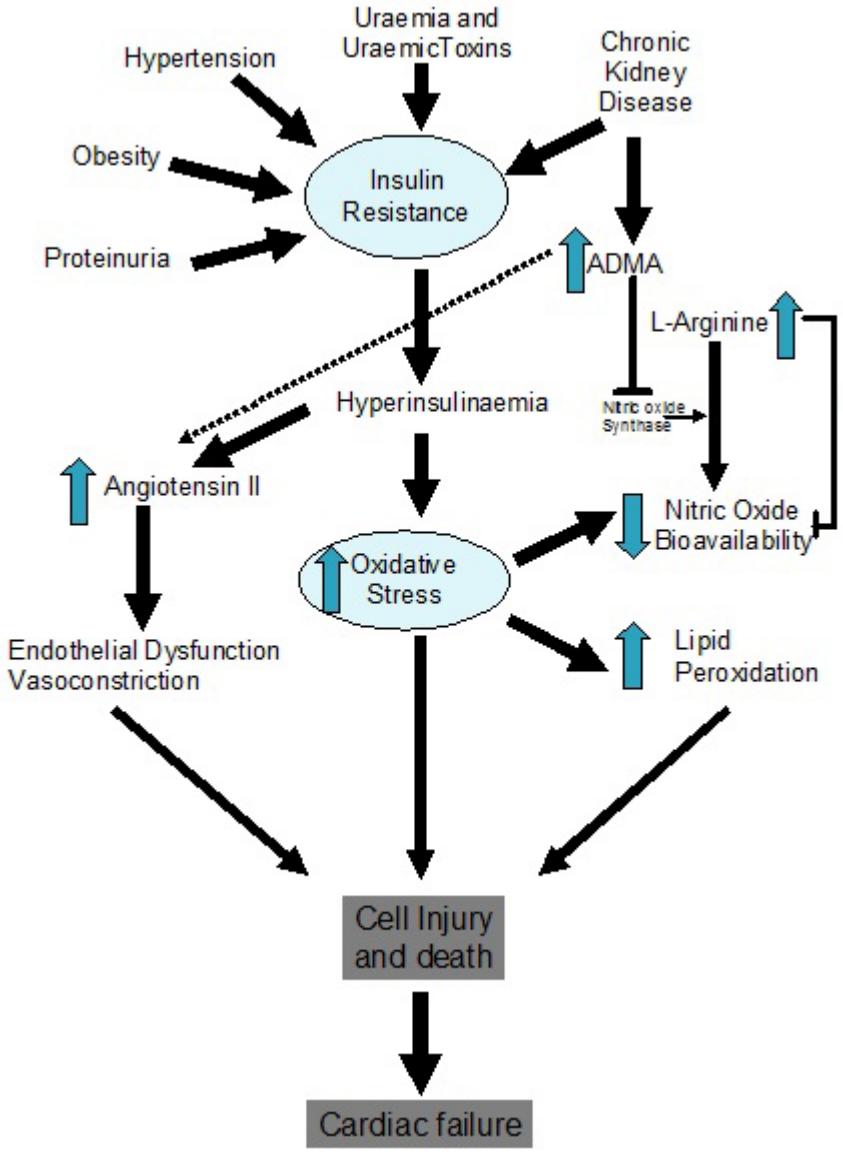

Figure 2. Summary of the potential interactions of insulin resistance and oxidative stress in cardiac disease (63-70). ADMA= asymmetric dimethylarginine

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 $(OH)_2$ 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 shiwn areduction in cytokine production (TNF-alpha, increased IL-10) and left ventricular mass in heart failure patients (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 uraemic 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 myoctye 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 myoctye contraction and relaxation. Recombinant erythropoietin may reduce myoctye apoptosis and hence cardiac fibrosis via phosphatidylinositol 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

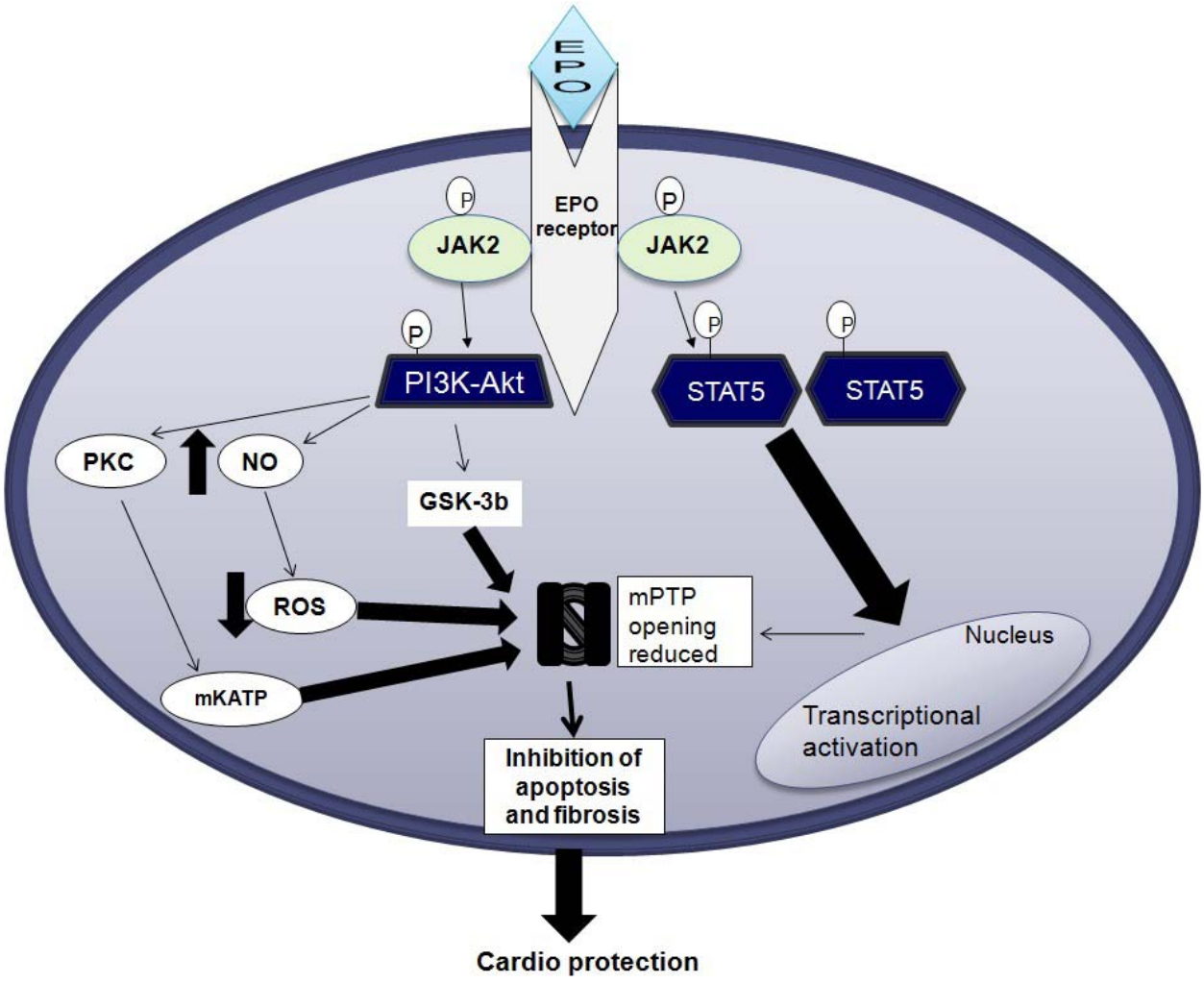

Figure 3. Schematic representation of the potential signalling pathway of Erythropoietin (EPO) mediated through its specific cellular receptor - EPO receptors. Once bound, EPO causes phosphorylation and subsequent activation of the receptor-associated Janus Kinase2 (JAk2) and activation of signalling 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, actinomyosin 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, hyperlipidemia, 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 uraemia 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 hyperocholesterolaemia 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

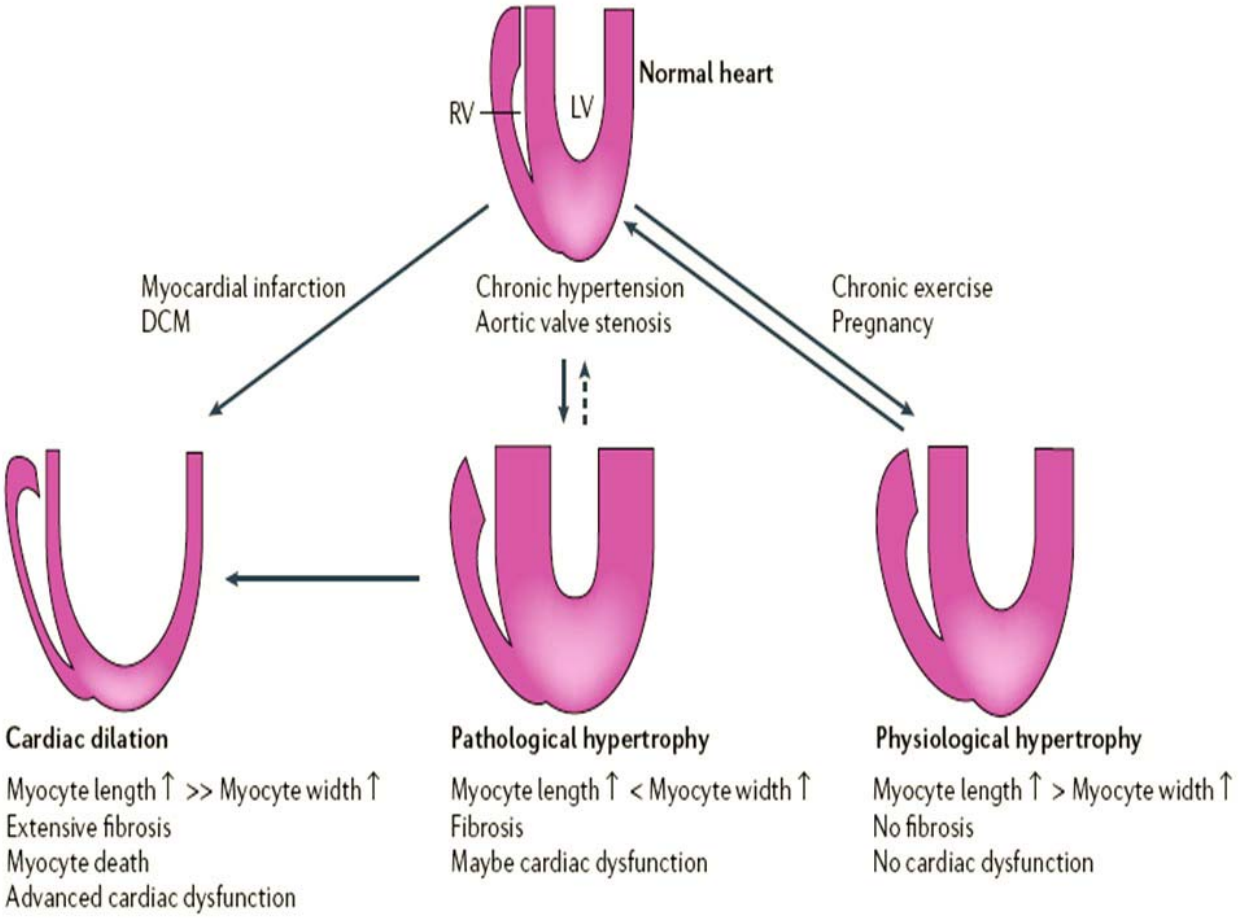

Figure 4. Types of cardiac hypertrophy: Physiological hypertrophy is characterised by a reversible, uniform hypertrophy in which muscle wall and chamber enlarge together without cardiac dysfunction. Pathological hypertrophy can be either concentric (thickening of chamber wall with reduction in chamber 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)

lumen) being observed in pressure overload states such as hypertension and an eccentric pattern (wall thickening but early LV dilatation) being associated with volume overloaded states such as anaemia (184, 185) (Figure 4). 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 myoctye 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). Pathological cardiac hypertrophy is characterized by contractile dysfunction, fibrosis and re-expression of fetal-type cardiac genes (191). Although macroscopic and cellular changes are evident, the hypertrophied heart is also associated with a multitude of complex biochemical and molecular alterations, which render the hypertrophied heart more susceptible to ischaemic injury and loss of cardio-myocytes through apoptosis contributing to ventricular dysfunction and the clinical syndrome of heart failure (192-194).

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

Pro-survival	Pro-death triggering apoptosis
JAK-STAT signalling	ROS
PIP(3)K - Akt signalling	Angiotensin II
Inhibition of cyclophilin D	Sympathetic stimulation
	Cytokines
	Increased cytosolic calcium
	Inflammation

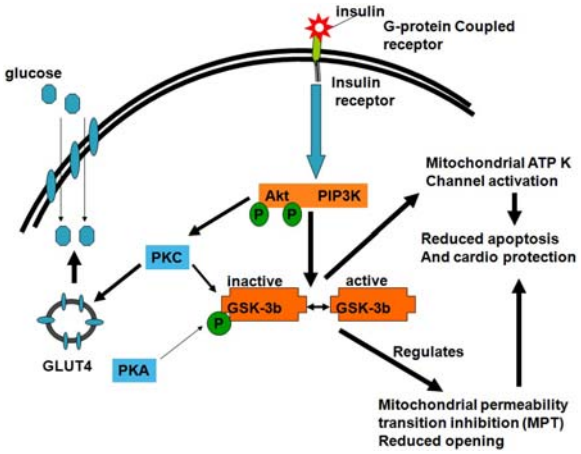

Figure 5. Akt-PIP3K pathways for insulin signalling. Insulin resistance decreases phospohrylation of Akt (protein kinase B) and sunsequently phosphorylation of GSK-3b (glycogen synthase kinase 3-beta). PKA = protein kinase A and PKC= protein kinase C

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 myoctye 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, endothelaial dysfunction, oxidative stress and cardiac disease still remain somewhat obscure. In formaulating a potential unifying pathway of cardiac risk in the development of uraemic cardiac disease, one might consider theb 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 vaso-pressin 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 myoctye cell survival mediated by the Akt-BAD (BcL2 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 naturetic 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 mianly epidemiological evidence indicates that treatment of mineral bone disease from a cardiovascular perspective may be beneficial. Cacium 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

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 Schneierson 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 iscaemic 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 a rosigltazone 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 leading to worsening of heart failure and potentially increased risk of myocardial infarction. The recent meta-analysis and results from the RECORD study suggest that there is no increased risk of cardiac death but a slight increased risk of heart failure in non uraemic patients (266-273). In uraemia they may be particularly beneficial, as in ESRD renal fluid and sodium homeostasis is less dependent on the kidneys (273).

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 perhexiline, 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).

7. ACKNOWLEDEMENTS

I would like to thanks Dr David Eadington for critically reviewing the article and his valuable input.

8. REFERENCES

1. A. Kottgen, S. D. Russell, L. R. Loehr, C. M. Crainiceanu, W. D. Rosamond, P. P. Chang, L. E. Chambless, and J. Coresh: Reduced Kidney Function as a Risk Factor for Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol* 18, 1307-1315 (2007)

2. J. Coresh, E. Selvin, L.A. Stevens, J. Manzi, J. W. Kusek, P. Eggers, F. Van Lente and A. S. Levey: Prevalence of Chronic Kidney Disease in the United. States. *JAMA* 298 (17), 2038-2047 (2007)

3. N. Richards, K. Harris, M. Whitfield, D. O'Donoghue, R Lewis, M. Mansell, S. Thomas, J. Townend, M. Eames and D. Marcelli: The impact of population-based identification of chronic kidney disease using estimated glomerular filtration rate (eGFR) reporting, *Nephrol Dial Transplant* 23(2), 556-61, (2008)

4. K. Farrington: UK Renal Registry Report 2008, in Chapter4: ESRD prevalent rates in 2007 in the UK: National and centre-specific analyses, *UK Renal Registry*, Bristol, UK 43-68 (2008)

5. M.R. Cowie, D.A. Wood, A.J. Coats, S.G. Thompson, V. Suresh, V. P.A. Poole-Wilson and G.C. Sutton: Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 83(5), 505-10 (2000)

6. H.L. Hillege, D. Nitsch D, M.A. Pfeffer, K. Swedberg, J.J. McMurray, S. Yu, C.B. Granger, E.L. Michelson, J. Ostergren, J.H. Cornel, D. de Zeeuw, S. Pocock and D.J. van Veldhusen: Candesartan in heart failure: renal function as a predictor of outcome in a broad spectrum of patients with heart failure. CHARM investigators. *Circulation* 13, 671-678 (2006)

7. R. de Silva, N.P. Nikitin, K.K.A. Witte, A.S. Rigby, K. Goode, S Bhandari, A.L. Clark and J.G.F. Cleland: Incidence of and recovery from renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: Contributing factors and relationship to prognosis. *Eur Heart J* 27(5), 569-581 (2006)

8. J.D. Harnett, R.N. Foley, G.M. Kent, P.E. Barre, D. Murray and P.S. Parfrey: Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors. *Kidney Int* 47, 884-890 (1995)

9. US Renal Data System: Annual data Report. Bethesda US Department of public Health and Human Service. *Public Health Service*. National Institutes of Health (2007)

10. A. Levin: Prevalence of cardiovascular damage in early renal disease. *Nephrol Dial Transplant* 16(Suppl 2), 7-11 (2001)
,
11. H.L. Hillege, A.R. Girbes, P.J. de Kam, F. Boomsma, D. de Zeeuw, A. Charlesworth, J. R. Hampton and D. J. van Veldhuisen: Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 102, 203-10 (2000)

12. D.L. Dries, D.V. Exner, M.J. Domanski, B. Greenberg and L.W. Stevenson: The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 35, 681-689 (2000)

13. J.V. Bhatai, S.D. Tu, P.C. Lee, F. Austin, A. Haouzi, Y Gong and P. P. Liu*:* Outcome of Heart Failure with Preserved Ejection Fraction in a Population-Based Study. *N Engl J Med* 355, 260-269 (2009)

14. S. Keith, G.A. Nichols, C.M. Gullion, J.B. Brown and D.H. Smith: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Archives of Internal Medicine* 164(6), 659-6304 (2004)

15. B.F. Culleton, M.G. Larson, P.W. Wilson, J.C. Evans, P.S. Parfrey and D. Levy: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 56(6), 2214-9 (1999)

16. R.N. Foley, P.S. Parfrey and M.J. Sarnak: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32(5 Suppl 3), S112-9 (1998)

17. A. Cherukuri and S. Bhandari: Analysis of risk factors for mortality of incident patients commencing dialysis in East Yorkshire, UK. *Quartery J Med* 33 (8), 41-48 (2009)

18. A. Lindner, B. Charra, D.J. Sherrard and B.H. Scribner: Accelerated atherosclerosis in prolonged maintenance hemodialysis, *N Engl J of Med* 290(13), 697-701 (1974)

19. S.G. Rostand, J.C. Gretes, K.A. Kirk, E.A. Rutsky and T.E. Andreoli: Ischemic heart disease in patients with uraemia undergoing maintenance hemodialysis. *Kidney Int* 16(5), 600-11 (1979)

20. S.G. Rostand, K.A. Kirk and E.A. Rutsky: Dialysis-associated ischemic heart disease: insights from coronary angiography. *Kidney Int* 25(4), 653-9 (1984)

21. N. Clyne L.E. Lins and S.K. Pehrsson: Occurrence and significance of heart disease in uraemia. An autopsy study. *Scand J Urol Nephrol* 20(4), 307-11 (1986)

22. U. Schwarz, M. Buzello, E. Ritz, G. Stein, G. Raabe, G. Wiest, G. Mall and K. Amann: Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant* 15(2), 218-23 (2000)

23. M. Briet, E. Bozec, S. Laurent, C. Fassot, G.M. London, C. Jacquot, M. Froissart, P. Houillier and P. Boutouyrie: Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int* 69(2), 350-7 (2006)

24. N. Dhaun, J. Goddard and D.J. Webb: The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol* 17, 943-955 (2006)

25. M. Sarraf, A. Masoumi and R.W. Schrier: Cardiorenal syndrome in acute decompensated heart failure. *Clin J Am Soc Nephrol* 4, 2013-2026 (2009)

26. E.H. Starling: Physiological factors involved in the causation of dropsy. *Lancet* 1, 1407-1410 (1896)

27. J.V. Warren and E.A. Stead Jr: Fluid dynamics in chronic congestive heart failure. *Arch Intern Med* 73, 138-147 (1944)

28. A. Al-Ahmad, W.M. Rand, G. Manjunath, M.A. Konstam, D.N. Salem, A.S. Levey and M.J. Sarnak: Reduced kidney function and anaemia as risk factors for mortality in patients with left ventricular dysfunction. *J AM Coll Cardiol* 38, 955-62 (2001)

29. C. Ronco, M. Haapio, A.A. House, N. Anavekar and R. Bellomo: Cardio-renal syndrome, *J Am Coll Cardiol* 52 (19), 1527-39 (2008)

30. G.S. Francis, C. Benedict, D.E. Johnston, P.C. Kirlin, J. Nicklas, C.S. Liang, S.H. Kubo, E. Rudin-Toretsky and S. Yusuf: Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a sub-study of the Studies of left Ventricular Dysfunction (SOLVD). *Circulation* 82, 1724-1729 (1990)

31. N.K. Hollenberg: Control of renal perfusion and function in congestive heart failure. *Am J Cardiol* 62(8), 72E-75E (1988)

32. H.R. Middlekauff, E.U. Nitzsche, C.K. Hoh, M.A. Hamilton, G.C. Fonarow, A. Hage and J.D. Moriguchi: Exaggerated renal vasoconstriction during exercise in heart failure patients. *Circulation* 101, 784-789 (2000)

33. W.H. Lee and M. Packer: Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation* 73(2), 257-267 (1986)

34. J. E. Sealey and J.H. Laragh: The renin-angiotensin-aldosterone system for normal regulation of blood pressure and sodium and potassium homeostasis. In: Laragh JH, Brenner BM, eds. Hypertension: pathophysiology, diagnosis and management. 2nd ed. Vol.2. New York: *Raven Press* 1763-1796 (1995)

35. M. Briet and E.L. Schiffrin: Aldosterone: effects on the kidney and cardiovascular system. *Nature Reviews* 6, 261-273 (2010)

36. C.S. Barr, C.C. Lang, J. Hanson, M. Arnott, N. Kennedy and A.D. Struthers: Effects of adding spironolactone to an angiotensin-conveting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 76, 1259-65 (1995)

37. C.A. Farquharson and A.D. Struthers: Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. *Circulation* 101, 594-7 (2000)

38. M. Epstein: Aldosterone as a determinant of cardiovascular and renal dysfunction. *J Royal Society Medicine* 94, 378-83 (2001)

39. K.T. Weber: Aldosterone in Congestive Heart Failure. *N Engl J Med* 345, 1689-1697 (2001)

40. J.G.G. Borst and A. Borst-DeGeus: Hypertension explained by Starling's theory of circulatory homeostasis. *Lancet* 1, 677 (1963)

41. H.R. Middlekauff, E.U. Nitzsche, C.K. Hoh, M.A. Hamilton, G.C. Fonarow, A. Hage and J.D. Moriguchi: Exaggerated renal vasoconstriction during exercise in heart failure patients. *Circulation* 101, 784-789 (2000)

42. W.T. Abraham, J.D. Port and M.R. Bristow: Neurohormonal receptors in the failing heart. In: Poole-Wilson PA, Colucci WS, Massie BM, Chatterjee K, Coats AJS, eds. Heart Failure. New York: *Churchill Livingstone* 127-141 (1997)

43. E. Bell-Reuss, D.L. Trevino and C.W. Gottschalk: Effect of renal sympathetic nerve stimulation on proximal water and sodium retention. *J Clin Invest* 57, 1104-1107 (1976)

44. S.R. Orth, K. Amann, K. Strojek and E. Ritz: Sympathetic overactivity and arterial hypertension in renal failure. *Nephrol Dial Transplant* 16 Suppl 1, 67-69 (2001)

45. V. Reddy, S. Bhandari and A.M. Seymour: Myocardial function, energy provision and carnitine deficiency in experimental uraemia. *J Am Soc Nephrol* 18 (1), 84-92 (2007)

46. W.C. F. Stanley, F.A. Recchia and G.D. Lopaschuk: Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 85, 1093-1129 (2005)

47. A.G. Marangou, F.P. Alford, G. Ward, F. Liskaser, P.M. Aitken, K.M. Weber, R.C. Boston and J.D. Best, Hormonal effects of norepinephrine on acute glucose disposal in humans, a minimal model analysis. *Metabolism* 37, 885-891 (1988)

48. L.H. Opie: The metabolic syndrome, does it exist? In Opie Kasuga M. Yellon DM, eds Diabetes at the limits. Vol 2 Cape town, South Africa. *University of Cape Town Press* 95-110 (2006)

49. G. Paolisso, A. Gambardella, D. GAlzerano, A. D'Amore, P. Rubino, M.Verza, P. Teasuro, M. Varricchio and F. D'Onofrio: Total body and myocardial substrate oxidation in congestive heart failure. *Metabolism* 43, 174-179 (1994)

50. R.M. Wittles, W.H. Tang, A.H. Jamali, J.W. Chu, G.M. Reaven and M.B. Fowler: Insulin resistance in idiopathic dilated cardiomyopathy: a possible etiologic link. *J Am Coll Cardiol* 44, 78-81 (2004)

51. A.E. Raine, A.M. Seymour, A.F. Roberts, G.K. Radda and J.G. Ledingham: Impairment of cardiac function and energetics in experimental renal failure. *J Clin Invest* 92(6), 2934-40 (1993)

52. J.S. Ingwall and R.G. Weiss: Is the failing heart energy starved? On using chemical energy to support cardiac function. *Circulation Research* 95, 135-145 (2004)

53. A.C. McMahon, G. Vescovo, L. Dalla, D.G. Wynne, R.J. Fluck, S.E. Harding and A.E. Raine: Contractile dysfunction of isolated ventricular myocytes in experimental uraemia. Exp Nephrol 4(3), 144-50 (1996)

54. A.C. McMahon, S.E. Greenwald, S.M. Dodd, M.J. Hurst and A.E. Raine: Prolonged calcium transients and myocardial remodelling in early experimental uraemia. Nephrol Dial Transplant 17(5), 759-64 (2002)

55. A.J. Murray, R.E. Anderson, G.C. Watson, G.K. Radda and K. Clarke: Uncoupling proteins in human heart. Lancet 364, 1786-1788 (2006)

56. M.E. Yung, P. McNulty and H. Taegtmyer: Adaptation and maladaptation of the heart in diabetes: part II: potential mechanisms. Circulation 105, 1861-1870 (2002)

57. J.J. McMurray and M.A. Pfeffer: Heart failure, Lancet 365(9474), 1877-891 (2005)

58. J. Marin-Garcia, M.J. Goldenthal and G.W. Moe: Mitochondrial pathology on cardiac failure. Cardiovasc Res 49, 17-26 (2001)

59. A. Garnier, D. Fortin, C. Delomenie, I. Momken, V. Veksler and R. Ventura-Clapier: Depressed mitochondrial transcription factors and oxidative capacity in rat failing cardiac and skeletal muscles. *J Physiol (Lond)* 551, 491-501 (2003)

60. V. Witko-Sarsat, M. Friedlander, T. Nhuyen Khoa, C. Capeillère-Blandin, A. T. Nguyen, S. Canteloup, J-M. Dayer, P. Jungers, T. Drüeke and B. Descamps-Latscha: Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. *J Immunol* 161, 2524-2532 (1998)

61. D.H. Endeman and E.L. Schiffrin: Endothelial dysfunction. *J Am Soc Nephrol* 15, 1983-1992 (2004)

62. S.R. Pieczenik and J. Neustadt: Mitochondrial dysfunction and molecular pathways of disease. *Exp Mol Pathol* 83, 84-89 (2007)

63. B.N. Becker, J. Himmelfarb, W.L. Henrich and R.M. Hakim: Reassessing the cardiac risk profile in chronic hemodialysis patients: a hypothesis on the role of oxidant stress and other non-traditional cardiac risk factors. *J Am Soc Nephrol* 51, 1669-1677 (1997)

64. S.M. Haffner: Clinical Relevance of the oxidative stress concept. *Metabolism* 49 (suppl 1), 30-34 (2000)

65. J.T. Kielstein and C. Zoccali: Asymmetric dimethylarginine: A cardiovascular risk factor and a uraemic toxin coming of age. *Am J kidney Dis* 46, 186-202 (2005)

66. K. Okubo, K. Hayashi, S. Wakino, H. Matsuda, E. Kubota, M. Honda, H. Tokuyama, T. Yamamoto, F. Kajiya and T. Saruta: Role of Dimerthylarginine in renal microvascular endothelial dysfunction in chronic renal failure with hypertension. *Hyperts Res* 28, 181-189 (2005)

67. S. Aslam, T. Santha, A. Leone and C. Wilcox: Effects of amlodipine and valsartan on oxidative stress and plasma methylarginines in end-stage renal disease patients on haemodialysis. *Kidney Int* 70, 2109-2115 (2006)

68. S. Moncada and A. Higgs: The L-arginine-nitric oxide pathway. *N Engl J Med* 329, 2002-2012 (1993)

69. L. De Nicola, R.C. Blantz and F.B. Gabbai: Nitric oxide and angiotensin II: glomerular and tubular interaction in the rat. *J Clin Invest* 89, 1248-1256 (1992)

70. U.C. Garg and A. Hassid: Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. *J Clin Invest* 83, 1774-1777 (1989)

71. U.C. Garg and A. Hassid: Inhibition of rat mesangial cell mitogenesis by nitric oxide-generating vasodilators. *Am J Physiol* 257, F60-F66 (1989)

72. T. Supaporn, S.M. Sandberg, D.D. Borgeson, D. M. Heublein, A. Luchner, C. Wei, T. P. Dousa and J.C. Burnett Jr: Blunted cGMP response to agonists and enhanced glomerular cyclic 3',5'-nucleotide phosphodiesterase activities in experimental congestive heart failure. *Kidney Int* 50, 1718-1725 (1996)

73. P. MacDonald, C. Schyvens and D. Winlaw: The role of nitric oxide in heart failure: potential for pharmacological intervention. *Drugs Aging* 8, 452-458 (1996)

74. R. Kennedy, C. Case, R. Fathi, D. Johnson, N. Isbel and T. H. Marwick: Does renal failure cause an atherosclerotic milieu in patients with end-stage renal disease? *Am J Med* 110, 198-204 (2001)

75. A. Calver, J. Collier, S. Moncada and P. Vallance: Effect of local intra-arterial NG-monomethyl-L-arginine in patients with hypertension: the nitric oxide dilator mechanism appears abnormal. *J Hypertension* 10, 1025-1031 (1992)

76. M.O. Ribero, E. Antunes, G. de Nucci, S.M. Lovisolo and R. Zatz: Chronic inhibition of nitric oxide synthesis: new models of arterial hypertension. *Hypertension* 20, 298-303 (1992)

77. A. Cerielli: Controlling oxidative stress as a novel molecular approach to protecting the vascular wall in diabetes. C*urrent Opinion in Lipidology* 17, 510-18 (2006)

78. P. Stenvinkel, O. Heimburger, T. Wang, B. Lindholm, J. Bergstrom and C.G. Elinder: High hyaluronan indicates poor survival in renal repalcement therapy. *Am J Kidney Dis* 34, 1083-1088 (1999)

79. M. Tong, J.J. Carrero, A.R. Qureshi, B. Anderstam, O. Heimburger, P. Stenvinkel, B. Lindholm and M.E. Suliman: Plasma pentraxin 3 in chronic kidney disease patient: Associations with renal function, protein-energy wasting, cardiovascular disease and mortality. *Clin J Am Soc Nephrol* 2, 889-897 (2007)

80. M.G. Shlipak, L.F. Fried, C. Crump, A.J. Bleyer, T.A. Manolio, R.P. Tracy, C.D. Furberg and B.M. Psaty: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107, 87-92 (2003)

81. J. Zimmmermann, S. Herrlinger, A. Pruy, T. Metzger and C. Wanner: Inflammation enhances cardiovascular risk and mortality in haemodialysis patients. *Kidney Int* 55, 648-658 (1999)

82. R. Pecoitis-Filho, B. Barany, B. Londholm, O. Heimburger and P. Stenvinkel: Interlukin-6 and its receptor is an independent predictor of mortality in patients starting dialysis treatment. *Nephrol Dial Transplant* 17, 1684-1688 (2002)

83. E.G. Lowrie and N.L. Lew: Death risk in haemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15, 458-482 (1990)

84. J. Himmelfarb, P. Stenvinkel, T.A. Ikizler and R.M. Hakin. The elephant of uraemia: oxidative stress as a unifying concept of cardiovascular disease in uraemia. *Kidney Int* 62, 524-1538 (2002)

85. U. Merle, E. Fein and S.G. Gehrke: The iron regulatory peptide hepcidin is expressed in the heart and regulated by hypoxia and inflammation. *Endocrinology* 148, 2663-2668, (2007)

86. W.G. Goodman, J. Goldin, B.D. Kuizon, C. Yoon, B. Gales, D. Sider, Y. Wang, J. Chung, A. Emerick, L. Greaser, R. M. Elashoff, and I. B. Salusky: Coronary artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342, 1478-1483 (2000)

87. G.M. London, B. Pannier, S.J. Marchais and A.P. Guerin: Calcification of the aortic valve in the dialysed patient. *J Am Soc Nephrol* 11, 778-783 (2000)

88. J.J. Mourad, X. Gererd, P. Boutouyrie, S. Laurent, M. Safar and G. London: Increased stiffness of radial artery wall material in end-stage renal disease. *Hypertension* 30, 1425-1430 (1997)

89. A. Ahmed, M.W. Rich, P.W. Sanders, G.J. Perry, G.L. Bakris, M.R. Zile, T.E. Love, I.B. Aban and M.G. Shilipak: Chronic kidney disease associated mortality in diastolic versus systolic heart failure: A propensity matched study. *Am J Cardiol* 99, 393-398 (2006)

90. A.G. Stack and W.E. Bloembergen: A cross-sectional study of the prevalence and clinical correlates of congestive heart failure among incident US dialysis patients. *Am J Kidney Dis* 38, 992-1000 (2001)

91. G.A. Block, T.E. Hubert-Shearon, N.W. Levin and F.K. Port: Association between serum phosphorus and calcium x phosphate product with mortality in chronic hemodialysis patients: a National Study. *Am J Kidney Dis* 31, 607-617 (1998)

92. C. Tomaijama, A. Higa, M.A. Delboni, M. Centorogalo, S.A. Draibe, L. Cuppen, A.B. Carvello, E.M. Neto and R.F. Canzianime: The impact of traditional and non-traditional risk factors on coronary calcification in CKD patients. *Nephrol Dial Transplant* 21, 2464-71 (2006)

93. M. Ketteler and P.H. Biggar: Getting the balance right: assessing causes and extent of vascular calcification in CKD. *Nephrology* 14, 389-394 (2009)

94. S.G. Rostand and T.B. Drueke: Parathyroid hormone, vitamin D and cardiovascular disease in chronic renal failure. *Kidney Int* 56, 383-392 (1999)

95. M. Wolf, A. Shah, O. Gutierrez, E. Ankers, M. Monroy, H. Tamez, D. Steele, Y. Chang, C.A. Camargo Jr, M. Tonelli and R Thadhani: Vitamin D levels and early mortality among incident haemodialysis patients. *Kidney Int* 72, 1004-1013 (2007)

96. M.R. Walters, T. Ilenchuk and W.C. Claycomb. 1,25-Dihydroxyvitamin D3 stimulates $45Ca_2^+$ uptake by cultured adult rat ventricular cardiac muscle cells: *J Biol Chem* 1987, 262, 2536-2541(1987)

97. S.G. Achinger and J. C. Ayus: The role of vitamin D in left ventricular hypertrophy and cardiac function. *Kidney Int* 67(suppl 95), S37–S42 (2005)

98. F. Galetta, A. Cupisti, F. Franzoni, F.R. Femia, M. Rossi, G. Barsotti and G. Santoro: Left ventricular function and calcium phosphate plasma levels in uraemic patients. *J Intern Med* 258, (7)4, 378-384 (2005)

99. M.A. Mirza, A. Larsson, H. Melhus, L. Lind and T.E. Larsson: Serum intact FGF-23 associated with LV mass, hypertrophy and geometry in elderly population. *Atherosclerosis* 5, 1010-1016 (2009)

100. G. Eknoyan and N.W. Levin: Impact of the new D/DOQI guidelines. *Blood Purif* 20, 103-108 (2002)

101. A. Levin and Y.C. Li: Vitamin analogues: Do they protect against cardiovascular disease in patients with kidney disease? *Kidney Int* 68, 1973-1981 (2005)

102. K. Kalantar-Zadeh, N. Kuwae, D.L. Regidor, C.P. Kovesdy, R.D. Kilpatrick, C.S. Shinaberger, C.J. McAllister, M.J. Budoff, I.B. Salusky and J.D. Kopple: Survival predictability of time-varying indicators of bone disease in maintenance haemodialysis patients. *Kidney Int* 70: 771-780 (2006)

103. P. Ravani, F. Malberti, G. Tripepi, P. Pecchini, S. Cutrupi, P. Pizzini, F. Mallamaci and C. Zoccali: Vitamin D levels and patient outcome in chronic kidney disease. *Kidney Int* 75, 88-95 (2009)

104. S.S. Schleithoff, A. Zittermann, G. Tenerich, H.K. Berthold, P Stehle and R. Koerfer: Vitamin D supplementation improved cytokine profiles in patients with congestive heart failure. A double blind, randomised, placebo-controlled trail. *Am J Clin Nutr* 83, 754-759 (2006)

105. M. Chonchol and R. Scragg: 25-hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. *Kidney Int* 71, 134-139 (2007)

106. D.J. Paulson and A.L. Shug: Experimental evidence of the anti-ischemic effect of L-carnitine, in de Jong JW FR (ed): The Carnitine System: A New Therapeutical approach to Cardiovascular Diseases. (Developments in Cardiovascular Medicine). Dordrecht, *Kluwer Academic Publishers* 183-198 (1995)

107. G.D. Lopaschuk, D.D. Belke, J. Gamble, T. Itoi and B.O. Schönekess: Regulation of fatty acid oxidation in the mammalian heart in health and disease. *Biochim Biophys Acta* 1213 (3), 263-76 (1994)

108. B.O. Schonekess and G.D. Lopaschuk: The effects of carnitine on myocardial carbohydrate metabolism, in de Jong JW, Ferrari R (eds): The Carnitine System: A New Therapeutical Approach to Cardiovascular Diseases. Dordrecht, *Kluwer Academic Publishers* 39-52 (1995)

109. G. Bellinghieri, D. Santoro, M. Calvani, G. Bellinghieri, D. Santoro, M. Calvani, A. Mallamace and V. Savica: Carnitine and hemodialysis. *Am J Kidney Dis* 41, S116-22 (2003)

110. A. Kobayashi A and S. Fujisawa: Effect of L-carnitine on mitochondrial acyl CoA esters in the ischemic dog heart. *J Mol Cell Cardiol* 26, 499-508 (1994)

111. J. Cui, D.K. Das, A. Bertelli and A. Tosaki: Effects of L-carnitine and its derivatives on postischemic cardiac function, ventricular fibrillation and necrotic and apoptotic cardiomyocyte death in isolated rat hearts. *Mol Cell Biochem* 254, 227-34 (2003)

112. P.Rizzon, G. Biasco, M. Di Biase, P. Rizzon, G. Biasco, M. Di Biase, F. Boscia, U. Rizzo, F. Minafra, A. Bortone, N. Siliprandi, A. Procopio, E. Bagiella and M. Corsi: High doses of L-carnitine in acute myocardial infarction: metabolic and anti-arrhythmic effects. *Eur Heart J* 10, 502-508 (1989)

113. S. Iliceto, D. Scrutinio, P. Bruzzi, G. D'Ambrosio, .L Boni, M. Di. Biase, G. Biasco, P.G. Hugenholtz, and P. Rizzon: Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial. *J Am Coll Cardiol* 26, 380-7 (1995)

114. A. Van Es, F.C. Henny, M.P. Kooistra, S. Lobatto and H.R. Scholte: Amelioration of cardiac function by L-carnitine administration in patients on haemodialysis. *Contrib to Nephrol* 98, 28-35 (1992)

115. D.S. Silverberg, D. Wexler, M. Blum, G. Keren, D. Sheps, E. Leibovitch, D. Brosh, S. Laniado, D. Schwartz, T. Yachnin, I. Shapira, D. Gavish, R. Baruch, B. Koifman, C. Kaplan, S. Steinbruch, and A. Iaina: The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anaemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 35, 1737-1744 (2000)

116. W.H. Horl, I.C. Macdougall, J. Rossert, B. Rutkowski, J.P. Wauters and F. Valderrabano: Predialysis survey on anaemia management: patient referral. *Am J Kidney Dis* 41, 49-61 (2003)

117. S. Bhandari and S. Naudeer: Improving efficiency and value in Health Care. Intravenous iron management for anaemia associated with chronic kidney disease. Linking treatment to an outpatient clinic, optimising service provision and patient choice. *Journal of Evaluation in Clinical Practice* 14(6), 996-1001 (2008)

118. S. Bhandari, A. Brownjohn and J.Turney: Effective utilisation of erythropoietin with intravenous iron therapy. *Journal of Clinical Pharmacy and Therapeutics* 23(1), 73-78 (1998)

119. R.N. Foley, P.S. Parfrey, J.D. Harnett, G.M. Kent, D.C. Murray and P.E. Barre: The impact of anaemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis* 28, 53-61 (1996)

120. F. Metivier, S.J. Marchais, A.P. Guerin, B. Pannier and G.M. London Pathophysiology of anaemia: focus on the heart and blood vessels. *Nephrol Dial Transplant* 15 Suppl 3, 14-18 (2000)

121. R, de Silva, A.S. Rigby, K.K. Witte, N.P. Nikitin, L. Tin, K. Goode , S. Bhandari, A.L. Clark and J.G. Cleland: Anaemia, Renal Dysfunction and their Interaction in Patients with Chronic Heart Failure. *Am J Cardiol* 98(3), 391-398 (2006)

122. D.S. Siverberg, D. Wexler, M. Blum, J.Z. Tchebiner, D. Sheps, C. Keren, D. Schwartz, R. Baruch, T. Yachnin, M. Shaked, I. Schwartz and I.A. Steinbrug: The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. *Nephrol Dial Transplant* 18(1), 141-146 (2003)

123. D.S. Silverberg, D. Wexler and D. Sheps, D. S. Silverberg, D. Wexler, D. Sheps, M. Blum, G. Keren, R. Baruch, D. Schwartz, T. Yachnin, S. Steinbruch, I. Shapira, S. Laniado, and A. Iaina: The effect of correction of mild anaemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 37, 1775-1780 (2001)

124. A.J. Bullard and D. M. Yellon: Chronic erythropoietin treatment limits infarct-size in the myocardium *in vitro*. *Cardiovasc Drugs Ther* 19(5), 333-6 (2005)

125. M. Y. Kim, M. J. Kim, M-Y Kim, M J Kim, I S Yoon, J H Ahn, S H Lee, E J Baik, C-H Moon and Y-S Jung: Diazoxide acts more as a PKC-epsilon activator, and indirectly activates the mitochondrial K(ATP) channel conferring cardioprotection against hypoxic injury. *Br J Pharmacol* 149(8), 1059-70 (2006)

126. D. Burger, M. Lei, D. Burger, M. Lei, N. Geoghegan-Mophet, X. Lu, A. Xenocostas and Q. Feng: Erythropoietin protects cardiomyocytes from apoptosis via up-regulation of endothelial nitric oxide synthase. *Cardiovasc Res* 72(1), 51-9 (2006)

127. K. Ohori, T. Miura, M. Tanno, T. Miki, T. Sato, S. Ishikawa, Y. Horio and K. Shimamoto: Ser9 phosphorylation of mitochondrial GSK-3-beta is a primary mechanism of cardiomyocyte protection by erythropoietin against oxidant-induced apoptosis. *Am J Physiol Heart Circ Physiol* 295, H2079–H2086 (2008)

128. K. Smith, D. Semple, S Bhandari and A.M. Seymour: Cellular basis of uraemic cardiomyopathy: a role for erythropoietin? *Eur J Heart Fail* 11(8), 732-8 (2009)

129. P.R. Hanlon, P. Fu, G.L. Wright, C. Steenbergen, M.O. Arcasoy and E. Murphy: Mechanisms of erythropoietin-mediated cardioprotection during ischemia-reperfusion injury: role of protein kinase C and phosphatidylinositol 3-kinase signaling. *FASEB J* 19, 1323–1325 (2005)

130. H.M. Razavi, J.A. Hamilton and Q. Feng: Modulation of apoptosis by nitric oxide: implications in myocardial ischemia and heart failure. *Pharmacol Ther* 106, 147-162 (2005)

131. R.S. Smith Jr, J. Agata, C.F. Xia, L. Chao and J. Chao: Human endothelial nitric oxide synthase gene delivery protects against cardiac remodeling and reduces oxidative stress after myocardial infarction. *Life Sci* 76, 2457–2471 (2005)

132. AMGEN: RED-HF Trial reduction of events with darbepoetin alfa in heart failure trial. 2007. *Http://clinialtrials.gov* accessed January 2010.

133. T.B. Drueke, F. Locatelli, N. Clyne, K.U. Eckardt, I.C. Macdougall, D. Tsakiris, H.U. Burger and A. Scherhag: Normalization of hemoglobin level in patients with chronic kidney disease and anaemia (CREATE). *N Engl J Med* 355, 2071–2084 (2006)

134. A.K. Singh, L. Szczech, K.L. Tang, H. Barnhart, S. Sapp, M. Wolfson and D. Reddan: Correction of anaemia with epoetin alfa in chronic kidney disease (CHOIR). *N Engl J Med* 355, 2085–2098 (2006)

135. M.A. Pfeffer, E.A. Burdmann, C.Y. Chen, M.E. Cooper, D. de Zeeuw, K.U. Eckardt, J.M. Feyzi, P. Ivanovich, R. Kewalramani, A.S. Levey, E.F. Lewis, J.B. McGill, J.J. McMurray, P. Parfrey, H.H. Parving, G. Remuzzi, A.K. Singh, S.D. Solomon, R. Toto and the TREAT Investigators: A Trial of Darbepoetin Alpha in type 2 diabetes and chronic kidney disaese (TREAT) *N Engl J Med* 361, 2019-2031 (2009)

136. G.E.M. Strippoli, G. Tognoni, S.D. Navaneethan, A. Nicholucci and J.C. Criag. Haemoglobin targets: we were wrong, time to move on *Lancet* 369, 349-350 (2007)

137. L. Blayney, R. Bailey-Wood, A. Jacobs, A. Henderson and J Muir: The effects of iron deficiency on the respiratory function and cytochrome content of rat heart mitochondria. *Circulation Research* 39, 744-748 (1976)

138. F.Z. Meerson and V.D. Pomoinitsky: The role of high-energy phosphate compounds in the development of cardiac hypertrophy. *J Mol Cell Cardiol* 4, 571-597 (1972)

139. X.E. Nemeth, M.S. Tuttle and J. Powelson: Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *J Science* 306(5704), 2051-2051 (2004)

140. E. Nemeth and T. Ganz: Hepcidin and iron loading anaemias. *Haematologica* 91, 727-732 (2006)

141. J. Zaritsky, B. Young, H. Wang, M. Westerman, G. Olbina, E. Nemeth, T. Ganz, S. Rivera A. R. Nissenson and I. B. Salusky: Hepcidin - A Potential Novel Biomarker for Iron Status in Chronic Kidney Disease. *Clin J Am Soc Nephrol* 4, 1051-1056 (2009)

142. B.M. Brenner, T.W. Meyer and T.H. Hostetter: Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation and intrinsic renal disease. *N Engl J Med* 307, 652-659 (1982)

143. G. Remuzziand and T. Bertani: Pathophysiology of progressive nephropathies. *N Engl J Med* 339, 1448-1456 (1998)

144. C.E. Mogensen: Microalbuminuria as a predictor of clinical diabetic nephropathy. *Kidney Int* 31, 673-689 (1982)

145. C.P. Shearman and P. Gosling: Microalbuminuria and vascular permeability. *Lancet* 2, 906-907 (1988)

146. B.M. Brenner, T.H. Hostetter and H.D. Humes: Molecular basis of proteinuria of glomerular origin. *N Engl J Med* 298, 826-833 (1978)

147. E.M. Damsgaard, A. Froland, O.D. Jorgensen and C.E. Mogensen. Microalbuminuria as predictor of increased mortality in elderly people. *BMJ* 300, 297-300 (1990)

148. K. Wachtell, V. Palmieri, M.H. Olsen, J.N. Bella, T. Aalto, B. Dahlof, E. Gerdts, J.T. Wright, V. Papademetriou, C.E. Mogensen, K. Borch-Johnsen, H. Ibsen and R.B. Devereux: Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study. *Am Heart J* 143, 319-326 (2002)

149. M. Abbate, C. Zoja, D. Corna, M. Capitanio, T. Bertani and G. Remuzzi: In progressive nephropathies, overload of tubular cells with filtered proteins translates glomerular permeability dysfunction into cellular signals of interstitial inflammation. *J Am Soc Nephrol* 9, 1213-1224 (1998)

150. R. Lapinski, N. Perico, A. Remuzzi, F. Sangalli, A. Benigni and G Remuzzi: Angiotensin II modulated glomerular capillary permselectivity in rat isolated perfused kidney. *J Am Soc Nephrol* 7, 653-660 (1996)

151. G. Wolf and E.G. Neilson: Angiotensin II as a renal growth factor. *J Am Soc Nephrol* 3, 1531-1540 (1993)

152. B.M. Zenere, G. Arcaro, F. Saggiani, L. Rossi, M. Muggeo and A. Lechi: Noninvasive detection of functional alterations of the arterial wall in IDDM patients with and without microalbuminuria. *Diabetes Care* 18, 975-982 (1995)

153. L. Niskanen, A. Turpeinen, I. Penttila and M.I. Uusitupa: Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis. *Diabetes Care* 21, 1861-1869 (1998)

154. S. Giaconi, C. Levanti, E. Fommei, F. Innocenti, G. Seghieri, L. Palla, C. Palombo and S. Ghione: Microalbuminuria and casual and ambulatory blood pressure monitoring in normotensives and in patients with borderline and mild essential hypertension. *Am J Hypertens* 2, 259-261 (1989)

155. L.M. Ruilope: The kidney as part of the cardiovascular system. *J Cardio Vasc Pharma* 33(Supple 1), S7-S10 (1999)

156. S. Bianchi, R. Bigazi and V.M. Campese: Microalbuminuria in essential hypertension: significance, pathophysiology, and therapeutic implications. *Am J Kidney Dis* 34, 973-995 (1999)

157. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis, *Lancet* doi:10.1016/S0140-6736(10) 60674-5 (2010)

158. X.B.R. Hemmeigam, BJ Manns and A Lloyd: Relation between kidney function, proteinuria, and adverse outcomes: *JAMA* 303 (5), 423-429 (2010)

159. T. Ninomiya, V. Perkovic, B.E. de Galan, S. Zoungas, A. Pillai, M. Jardine, A. Patel, A. Cass, B. Neal, N. Poulter, C-E. Mogensen, M. Cooper, M. Marre, B. Williams, P. Hamet, G. Mancia, M. Woodward, S. MacMahon, J. Chalmers on behalf of the ADVANCE Collaborative Group: Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes *J Am Soc Nephrol* 20, 1813-1821 (2009)

160. M. Arnadottir, B. Hultberg, P. Nilsson-Ehle and H. Thysell: The effect of reduced glomerular filtration rate on plasma total homocysteine concentration. *Scand J Clin Lab Invest* 56, 41-46 (1996)

161. B.L. Urquhartt and A.A. House: Assessing plasma total homocysteine in patients with end-stage renal disease *Perit Dial Int* 27, 476-488 (2007)

162. C.J. Boushey, S.A.A. Beresford, G.S. Omenn and A.G. Motulsky: A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. *JAMA* 274, 1049-1057 (1995)

163. A. Tawakol, O. Torbjorn, M. Gerhard, J.T. Wu and M.A. Creager: Hyperhomocysteinemia is associated with impaired endothelium-dependent vasodilation in humans. *Circulation* 95, 1119-1121 (1997)

164. J.C. Tsai, M.A. Perrella, M. Yoshizumi, C.M. Hsieh, E. Haber, R. Schlegel and M.E. Lee: Promotion of vascular smooth muscle cell growth by homocysteine: A link to atherosclerosis. *Proc Natl Acad Sci* 91, 6369-6373 (1994)

165. J. Loscalzo: The oxidant stress of hyperhomocysteinemia. *J Clin Invest* 98, 5-7 (1996)

166. R.L. Jamison, P. Hartigan, J.S. Kaufman, D.S. Goldfarb, S.R. Warren, P.D. Guarino and J.M. Gaziano: Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end stage renal disease. A randomised controlled trail *JAMA* 298, 1163-1170 (2007)

167. J. Heinz, S. Kropf, U. Domröse, S. Westphal, K Borucki, C Luley, K.H. Neumann and J. Dierkes: B vitamins and the risk of total of total mortality abd cardiovascular disease: results of a randomized controlled trial. *Circulation* 30, 1432-1438 (2010)

168. F.H. Messerli, E.D. Fhrolich, G.R. Dreslinski, D.H. Suarez and C.G. Aristimuno: Serum uric acid in essential hypertension: an indicator of renal vascular involvement. *Ann Intern Med* 93, 817-812 (1980)

169. L.E. Spieker, F.T. Ruschitzka, T.F. Luscher and G. Noll: The management of hyperuricemia and gout in patients with heart failure. *Eur J Heart Failure* 4, 403-410 (2002)

170. M.M.T, Fuh, C.M. Lee, C.Y. Jeng, D-C. Shen, S-M. Sheih, G.M. Reaven and Y-D Chen: Effect of chronic renal failure on high-density lipoprotein kinetics. *Kidney Int* 37, 1295-1300 (1990)

171. D.J. Gordon, J.L. Probstfield, R.J. Garrison, J.D. Neaton, W.P. Castelli, J.D. Knoke, D.R. Jacobs Jr, S. Bangdiwala and H.A Tyroler: High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation* 79, 8-15 (1989)

172. M. Koch, B. Kutkuhn, E. Trenkwalder, D. Bach, B. Grabensee, H. Dieplinger and F. Kronenberg: Apolipoprotein B, fibrinogen, HDL cholesterol, and apolipoprotein (a) phenotypes predict coronary artery disease in hemodialysis patients. *J Am Soc Nephrol* 8, 1889-1898 (1997)

173. P. Attman and P. Alaupovic: Abnormalities of lipoprotein composition in renal insufficiency. *Prog Lipid Res* 30, 275-9 (1991)

174. B.C. Kwan, F. Kronenberg, S. Beddhu and A.K. Cheung: Lipoprotein metabolism and lipid management in chronic kidney disease. *J Am Soc Nephrol* 18, 1246-1261 (2007)

175. M.E. Rischmann, F. Kronenberg, E. Trenkwalder, J.R. Schaefer, H. Schweer, B. Dieplinger, P. Koeniig, K. Ikewaki K and H. Dieplinger: *In vivo* turnover study demonstrates diminished clearance of lipoprotein (a) in haemodialysis patients *Kidney Int* 71, 1036-1043 (2007)

176. L.A. Sechi, L. Zingaro, S. DeCarli S, G. Sedchi, C.Catena, E. Falleti, E. Dell'Anna and E. Bartoli: Increased

serum lipoprotein(a) levels in patients with early renal failure. *Ann Int Med* 129, 457-461 (1998)

177. J. Danesh, R. Collins and R. Peto: Lipoprotein (a) and coronary heart disease: meta-analysis of prospective studies. *Circulation* 102, 1082-1088 (2000)

178. M.M. Avram, P. Goldwasser, D.E. Burrell, A. Antignani, P.A. Fein and N. Mittman: The uraemic dyslipidemia: a cross-sectional and longitudinal study. *Am J Kidney Dis* 20(4), 324-35 (1992)

179. C. Wanner, V. Krane, M. Winfried, M. Olschewki, J.F.E. Mann, G. Ruf and E. Ritz: Atorvostatin in patients with type 2 diabetes mellitus undergoing haemodialysis. *N Engl J Med* 353, 238-248 (2005)

180. B.C. Fellström, A.G. Jardine, R.E. Schmieder, H. Holdaas, K.Bannister, J. Beutler, D.W. Chae, A. Chevaile, S.M. Cobbe, C. Grönhagen-Riska, J.J. De Lima, R. Lins, G. Mayer, A.W. McMahon, H.H. Parving, G. Remuzzi, O. Samuelsson, S. Sonkodi, D. Sci, G. Süleymanlar, D. Tsakiris, V. Tesar, V. Todorov, A. Wiecek, R.P. Wüthrich, M. Gottlow, E. Johnsson, F. Zannad and AURORA Study Group: Rosuvastatin and cardiovascular events in patients undergoing hemodialysis, *N Engl J Med* 360(14), 1395-407 (2009)

181. S.D. Navaneethan, F. Pansini, V. Perkovic, C. Manno, F. Pellegrini, D.W. Johnson, J.C. Craig and G.F. Strippoli: HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis, *Cochrane database of systematic reviews (Online)*(2), CD007784 (2009)

182. F.K. Port: Morbidity and mortality in dialysis patients. *Kidney Int* 46, 1728-1737 (1994)

183. A. Levin, J. Singer and C.R. Thomson: Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis* 27, 347-354 (1996)

184. R. Foley, P. Parfrey and J.D. Harnett: The prognostic importance of left ventricular geometry in uraemic cardiomyopathy. *J Am Soc Nephrol* 5, 2024 (1995)

185. J. Heineke and J.D. Molkentin: Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nat Rev Mol Cell Biol* 7(8), 589-600 (2006)

186. L. Mazzolai, J. Nussberger, J.F. Aubert, D.B. Brunner, G. Gabbiani, H.R. Brunner and T. Pedrazzini. Blood pressure-independent cardiac hypertrophy induced by locally activated renin-angiotensin system. *Hypertension* 31, 1324-1330 (1998)

187. K. Amann and E. Ritz: Cardiac structure and function in renal disease, *Curr Opin Nephrol Hypertens* 5(1), 102-6 (1996)

188. K. Amann, G. Wiest, G. Zimmer, N. Gretz, E. Ritz and G.Mall: Reduced capillary density in the myocardium of uraemic rats-a stereological study. *Kidney Int* 42(5), 179-85 (1992)

189. D. Levy, M.G. Larson, R.S. Vasan, W.B, Kannel and K.K.L Ho: The progression from hypertension to congestive heart failure. *JAMA* 275, 1557-1562 (1996)

190. R. Dikow, C. Wasserhess, K. Zimmerer, L.P. Kihm, M. Schaier, V Schwenger, S. Hardt, C. Tiefenbacher, H. Katus, M. Zeier and L.M.Gross: Effect of insulin and glucose infusion on myocardial infarction size in uraemic rats. *Basic Res Cardiol* 104(5), 571-9 (2009)

191. E. Braunwald and M.R. Bristow: Congestive heart failure: fifty years of progress. *Circulation* 102(20 Suppl 4), 14-23 (2000)

192. P. Anversa, J. Kajstura and G. Olivetti: Myocyte death in heart failure. *Curr Opin Cardiol* 11(3), 245-51 (1996)

193. R.S. Foo, K. Mani and R.N. Kitsis: Death begets failure in the heart. *J Clin Invest* 115(3), 565-71 (2005)

194. A.K. Sharma, S. Dhingra, N. Khaper and P.K. Singal: Activation of apoptotic processes during transition from hypertrophy to heart failure in guinea pigs. *Am J Physiol Heart Circ Physiol* 293(3), H1384-90 (2007)

195. G.A. Kaysen: Disorders in high-density metabolism with insulin resistance and chronic kidney disease. *J Ren Nutr* 17(1), 4-8. (2007)

196. J.R. Sowers, P.R. Stanley, J.L. Ram, S. Jacober, L. Simpson and K. Rose: Hyperinsulinemia, insulin resistance and hyperglycemia: contributing factors in the pathogenesis of hypertension & atherosclerosis. *Am J Hypertens* 6, 260S-270S (1993)

197. D. Fliser, G. Pacini, R. Engelleiter, D. Fliser, G. Pacini, R. Engelleiter, A. Kautzky-Willer, R. Prager, E. Franek and E. Ritz: Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. *Kidney Int* 53, 1343-1347 (1998)

198. K. Shinihara, T. Shoji, M. Emoto, H. Tahara, H. Koyama, E. Ishimura, T. Miki, T. Tabata and Y. Nishizawa: Insulin resistance as an Independent predictor of cardiovascular mortality in patients with end stage renal disease. *J Am Soc Nephrol* 132, 1894-1900 (2002)

199. G.M. Reaven, H. Lithell and L. Landsberg: hypertension and associated metabolic abnormalities-the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 334, 374-381 (1996)

200. D.D. Belke, S. Betuing, M.J. Tuttle, C. Graveleau, M.E. Young, M. Pham, D Zhang, R.C. Cooksey, D.A. McClain, S.E. Litwin, H. Taegtmeyer, D. Severson, C.R. Kahn, and E.D. Abel: Insulin signaling coordinately regulates cardiac size, metabolism, and contractile protein isoform expression. *J Clin Invest* 109 (5), 629-39 (2002)

201. J. Chatham and A.M. Seymour: Cardiac carbohydrate metabolism in Zucker diabetic fatty rats. *Cardiovasc Res* 55(1), 104-112 (2002)

202. D. Semple, K. Smith, S. Bhandari and A.M. Seymour: Uremic Cardiomyopathy and Insulin Resistance: A Critical Role for Akt? *J Am Soc Nephrol* doi:10:1681ASN2009090900 (2010)

203. D. Aksentijević, S. Bhandari and A.M. Seymour: Insulin resistance and altered glucose transporter 4 expression in experimental uraemia. *Kidney Int* 75(7), 711-8 (2009)

204. D. Semple, S Bhandari and A.M. Seymour: Alterations in the insulin-RISK axis in uraemic cardiomyopathy. *J Am Soc Nephrol* 20(8), 279, (PO723) (2009)

205. H. Ashrafian, M.P. Frenneaux and L.H. Opie: Metabolic mechanisms in heart failure. *Circulation* 116, 434-448 (2007)

206. J. Hamilton, G.T. Chew and G. A. Watts: Therapeutic regulation of endothelial dysfunction in type 2 diabetes mellitus. *Diabetes and Vascular Disease Research* 4 (2), 89-102 (2007)

207. I.S. Anand and V.G. Florea: Diuretics in chronic heart failure-benefits and hazards. *Eur Heart J Supplements* 3 (Supple G), G8-G18 (2001)

208. The Digitalis Investigation Group: The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 336, 525-533 (1997)

209. CIBIS II Investigational Committees: The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet* 353, 9-13 (1990)

210. Effect of metoprolol CR/XL in chronic heart failure. Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 353, 2001-2007 (1999)

211. T.R. Walhaus, M. Taylor, T.R. DeGrado, D.C. Russell, P. Stanko, R.J. Nickles and C.K. Stone: Myocardial free fatty acid and glucose use after carveilol treatment in patients with congestive heart failure. *Circulation* 103, 2441-2446 (2001)

212. Al Hesayen, E.R. Azevedo, J.S. Floras, S. Hollingshead, G.D. Lopaschuk and J.D. Parker JD: Selective versus non-selective beta-adrenergic receptor blockade in chronic heart failure: differential effects on myocardial energy substrate utilisation. *Eur J Heart Fail* 7, 618-623 (2005)

213. The SOLVD investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 325, 293-302 (1991)

214. The CONSENSUS Trial Study Group: Effects of Enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 316, 1429-1435 (1987)

215. K. Swedberg, P. Held, J. Kjekshus, K. Rasmussen, L. Ryden and H. Wedel: Effects of the early administration of enalapril onmortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 327, 678-684 (1992)

216. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators: Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 342, 821-828 (1993)

217. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of an angiontensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 342, 145-153 (2000)

218. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355, 253-9 (2000)

219. E.L. Schriffrin and L.Y. Deng. Comparison of the effects of angiotensin I-converting enzyme inhibition and beta-blockade for 2 years on function of small arteries from hypertensive patients. *Hypertension* 25, 699-703 (1995)

220. B. Schieffer, E. Schieffer, D. Hilfiker-Kleiner, A. Hilfiker, P. T. Kovanen, M. Kaartinen, J. Nussberger, W. Harringer and H. Drexler: Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: potential implications for inflammation and plaque instability. *Circulation* 101, 1372-1378 (2000)

221. M.A. Pfeffer, J.M. Pfeffer, C. Steinber and P. Finn: Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril. *Circulation* 72, 406 (1985)

222. J.M. Pfeffer, M.A. Pfeffer and E. Braunwald: Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circulation Research* 57, 84 (1985)

223. B. Dahlof, K. Pennert and L. Hansson: reversal of left ventricular hypertrophy in hypertensive patients: a meta-analysis of 109 treatment studies. *Am J Hypertens* 5, 95-110 (1992)

224. I. Sihm, A.P. Shroeder and C. Aalkjaer: Regression of media-to-lumen ratio of human subcutaneous arteries and left ventricular hypertrophy during treatment with an angiotensin-converting enzyme

inhibitor based regimen in hypertensive patients. *Am J Cardiol* 76, 38E-40E (1995)

225. K. Rakusan, M.F. Flanagan, T. Geva, J. Southern, R and Van Praagh: Morphometry of human coronary capillaries during normal growth and the effect of age in left ventricular pressure-overload hypertrophy. *Circulation* 86, 8-46 (1992)

226. B. Pitt, R. Segal, F.A. Martinez, G. Meurers, A.J. Cowley, I. Thomas on behalf of ELITE study investigators: Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan InThe Elderly study; ELITE). *Lancet* 349, 747-752 (1997)

227. P. Vanhoutte: Endothelial dysfunction and inhibition of converting enzyme. *Eur Heart J* 19 (Suppl J), J7-J15 (1998)

228. B. Pitt, F. Zannad, W.J. Remme, R. Cody, A. Castaigne, A. Perez, J. Palensky and J. Wittes: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 341, 701-717 (1999)

229. B. Pitt, W. Remme, F. Zannad, J. Neaton, F. Martinez, B. Roniker, R. Bittman, S. Hurley, J. Kleiman, M. Gatlin for the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 348, 1309-21 (2003).

230. J.E. MacDonald, N. Kennedy and A.D. Struthers: Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. *Heart* 90, 765-7 (2004)

231. S.J.C. Longenecker, J. Coresh, N.R. Powe, A.S. Levey, N.E. Fink, A. Martin and M.J. Klag: Traditional cardiovascular disease risk factors in dialysis patients compared with the general population. The CHOICE study. *J Am Soc Nephrol* 13, 1918-1927 (2002)

232. M.S. Zhou, I. H. Schuman, E. A. Jaimes and L.Raij: Renoprotection by statins is linked to a decrease in renal oxidative stress, TGF-beta, and fibronectin with concomitant increase in nitric oxide bioavailability; *Am J Physiol - Renal Physiol* 295, f53-f59 (2008)

233. S. Shurraw and M. Tonelli: Statins for treatment of dyslipidaemia in chronic kidney disease. *Perit Dial Int* 26, 523-539 (2006)

234. C. Baigent and M. Landry. Study of heart and renal protection (SHARP) *Kid Int* Suppl, 207-210 (2003)

235. J.O. Mudd and D.A. Kass: Tackling heart failure in the twenty-first century. *Nature* 451, 919-928 (2008)

236. J.E. Udelson, W.B. Smith, G.H. Hendrix, C.A. Painchaud, M. Ghazzi, I. Thomas, J.K. Ghali, P. Selaru, F. Chanoine, M.L. Pressler and M.A. Konstam: Acute haemodyanmic effects of conivaptan, a dual V1A and V2 vasopressin receptor antagonist in patients with advanced heart failure. *Circulation* 104, 2417-2423 (2001)

237. P.S. Chan, J. Coupet, H.C. Park, F. Lai, D. Hartupee, P. Cervoni , J.P. Dusza, J.D. Albright, X. Ru, H. Mazandarani, T. Tanikella, C. Shepherd, L. Ochalski, T. Bailey, T.Y. Lock, X. Ning, J.R. Taylor and W. Spinelli: VPA-985, a nonpeptide orally active and selective vasopressin V2 receptor antagonist. *Adv Exp Med Biol* 449, 439-443 (1998)

238. R.M. Mills, T.H. LeJemtel, D.P. Horton, C. Liang, R. Lang, M.A. Silver, C. Lui, K. Chatterjee on behalf of the Natrecor Study Group: Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure. *J Am Coll Cardiol* 34, 155-162 (1999)

239. W.S. Colucci, U. Elkayam, D.P. Horton, W.T. Abraham, R.C. Bourge, A.D. Johnson, L.E. Wagoner, M.M. Givertz, C.S. Liang, M. Neibaur, W.H. Haught and T.H. LeJemtel: Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med* 343(4), 246-253 (2000)

240. J. E. Tobilli, A. Lombrana, P. Duarte and F. Di Gennaro: Intravenous iron reduces NT-Pro-brain naturetic peptide in anaemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol* 50(17), 1657-1665 (2007)

241. L.S. Marcus, D. Hart, M. Packer, Yushak, N. Medina, R. S. Danziger, D. F. Heitjan, and S. D. Katz: Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: a double-blind, palcebo-controlled, randomized crossover trial. *Circulation* 94, 3184-3189 (1996)

242. H.H. Chen, J.A. Grantham, J.A. Schirger, M. Jougasaki, M.M. Redfield and J.C. Burnett jr: Subcutaneous administration of brain natriuretic peptide in experimental heart failure. *J Am Coll Cardiol* 36, 1706-1712 (2000)

243. D.R. McClean, H. Ikram, A.H. Garlick, A. M. Richards, M. G. Nicholls, and I. G. Crozier: The clinical, cardiac, renal, arterial and neurohormonal effects of omapatrilat, a vasopeptidase inhibitor, in patients with chronic heart failure. *J Am Coll Cardiol* 36, 479-486 (2000)

244. J.L. Rouleau , M.A. Pfeffer, D.J. Stewart, D. Isaac, F. Sestier, E.K. Kerut, C.B. Porter, G. Proulx, C. Qian and A.J. Block: Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 356, 615-620 (2000)

245. J.C. Burnett: Vasopeptidase inhibition. *Curr Opin Nephrol Hypertens* 9, 465-468 (2000)

246. S.S. Gottlieb, D.C. Brater, I. Thomas, E. Havranek, R. Bourge, S. Goldman, F. Dyer, M. Gomez, D. Bennett, B. Ticho, E. Beckman and W.T. Abraham: BG9719 (CVT-124), an A1 Adenosine Receptor Antagonist, Protects Against the Decline in Renal Function Observed With Diuretic Therapy. *Circulation* 105, 1348-1353 (2002)

247. S. Sakai, T. Miyauchi, M. Kobayashi, I. Yamaguchi, K. Goto and Y.Sugishita: Inhibition of myocardial endothelin pathway improves long-term survival in heart failure. *Nature* 384, 353-355 (1996)

248. P. Boekstegers, S. Weidenhofer, R. Zell, P. Boekstegers, S. Weidenhöfer, R. Zell, G. Pilz, E. Holler, W. Ertel, T. Kapsner, H. Redl, S. Heinz, K. Günther, M. Kaul, J. Kempeni, R. Stenzel and K. Werdan: Repeated administration of a F(ab')2 fragment of an anti-tumor necrosis factor alpha monoclonal antibody in patients with severe sepsis: effects on the cardiovascular system and cytokine levels. *Shock* 1, 237-245 (1994)

249. S.D. Ankers, J. Comin Colet, G. Filippatos, R. Willenheimer, K. Dickstein, H. Drexler, T.F. Luscher, B. Bart, W. Banasiak, J. Niegowska, B. Kirwan, C. Mori, B. von Eisenhart Rothe, J.J. Pocock, R. Poole-Wilson for FAIR-HF Trial: Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 361, 2436-2448 (2009)

250. R.A. Zager: Parenteral iron compounds: potent oxidants but mainstays of anaemia management in chronic renal disease. *Clin J Am Soc Nephrol* 1 (suppl1), S24-S31 (2006)

251. D. Russo, I. Miranda, C. Ruocco, Y. Battaglia, E. Buonanno, S. Manzi, L. Russo, A. Scafarto and V.E. Andreucci: The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int* 72, 1255-1261 (2007)

252. A. Sharma, D.D. Hermann and R.L. Mehta: Clinical benefit and approach of ultrafiltration in acute heart failure. *Cardiology* 96(3-4), 144-154 (2001)

253. S.J. Schneierson: Continuous peritoneal irrigation in the treatment of intractable ooedema of cardiac origin. *Am J Med Sci* 218, 76-79 (1949)

254. Dileo, S. Bergerone, R. Pozzi, A. Pacitti, G. Tognarelli, G. Segoloni, A. Vercellone and A. Brusca: Ultrafiltration in the treatment of refractory congestive heart failure. *Clin Cardiol* 11, 449-452 (1988)

255. V. Tormey, P.J. Conlon, J. Farrell, J. Horgan and J.J. Walshe: Long-term successful management of refractory congestive cardiac failure by intermittent ambulatory peritoneal ultrafiltration. *Quarterly J Med* 89, 681-68310-11 (1996)

256. P. Konig, D. Geissler, P. Lechleitner, M. Spielbergerand P. Dittrich: Improved management of congestive heart failure. Use of continuous ambulatory peritoneal dialysis. *Arch Intern Med* 147, 1031-1034 (1987)

257. L.U. Mailloux, C.D. Swartz, G. Onesti, C. Heider, O. Ramirez, and A.N. Brest: Peritoneal dialysis for refractory congestive heart failure. *JAMA* 199, 873-878 (1967)

258. J.P. Ryckelynck, T. Lobbedez, B. Valette, C. Le Goff, O. Mazouz, B. Levaltier, J. Potier, and B. Hurault de Ligny: Peritoneal ultrafiltration and refractory congestive heart failure. *Nephrol Dial Transplant* 13 (suppl 4), 56-59 (1998)

259. M. Elhalel-Dranitzki, D. Rubinger, A. Moscovici, Y.S. Haviv, M.M. Friedlander, J. Silver and M.M. Popovtzer: CAPD to improve quality of life in patients with refractory heart failure. *Nephrol Dial Transplant* 13, 3041-3042 (1998)

260. B.G. Stegmayr, R. Banga, L. Lundberg, A.M. Wikdahl and M. Plum-Wirell: Peritoneal Dialysis treatment for severe congestive heart failure. *Perit Dial Int* 16 (suppl 1), 231-235 (1996)

261. B. Canaud, M. Leblanc, H. Leray-Moragues, S. Delmas, K. Klouche and J.J. Beraud: Slow continuous and daily ultrafiltration for refractory congestive heart failure. *Nephrol Dial Transplant* 13(suppl 4) 51-55 (1998)

262. S. Neubauer: The failing heart- an engine out of fuel. *N Engl J Med* 356, 1140-51. (2007)

263. H. Taegtmeyer: Energy metabolism of the heart: from basic concepts to clinical applications. *Curr Contib Cardiol* 19, 59-113 (1994)

264. J. O. Burton, H. J. Jefferies, N. M. Selby and C.W. McIntyre: Haemodialysis –induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol* 4, 1925-1931 (2009)

265. H. Ito, A. Nakano, M. Kinoshita and A. Matsumori: Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, attenuates myocardial ischemia/reperfusion injury in a rat model. *Lab Invest* 83(12), 1715-21 (2003)

266. P.D. Home, S.J, Pocock, H. Beck-Nielsen, P.S. Curtis, R. Gomis, M. Hanefeld, N.P. Jones, M. Komajda, J.J. McMurray and RECORD Study Team: Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 373(9681), 2125-35 (2009)

267. J.A. Dormandy, B. Charbonnel, D.J. Eckland, E. Erdmann, M Massi-Benedetti, I.K. Moules, A.M. Skene, M.H. Tan, P.J. Lefèbvre, G.D. Murray, E. Standl, R.G. Wilcox, L. Wilhelmsen, J. Betteridge, K. Birkeland, A. Golay, R.J. Heine, L Korányi, M. Laakso, M. Mokán, A. Norkus, V. Pirags, T. Podar, A.Scheen, W. Scherbaum, G. Schernthaner, O. Schmitz, J. Skrha, U. Smith, J Taton and PROactive investigators: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial

In macroVascular Events): a randomised controlled trial. *Lancet* 366(9493), 1279-89 (2005)

268. I.J. Dahabreh, and K. Economopoulos: Meta-analysis of rare events: an update and sensitivity analysis of cardiovascular events in randomized trials of rosiglitazone, *Clin Trials* 5(2), 116-20 (2008)

269. E. Erdmann and R.G. Wilcox: Weighing up the cardiovascular benefits of thiazolidinedione therapy: the impact of increased risk of heart failure. *Eur Heart J* 29(1), 12-20 (2008)

270. P.C. Satfylas, P.A. Sarafidis, and A.N. Lasaridis: The controversial effects of thiazolidinediones on cardiovascular morbidity and mortality. *International J of Cardiol* 131(3), 298-304 (2009)

271. S.E. Nissen and K. Wolski: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356(24), 2457-71 (2007)

272. S.P. Ramirez, J.M. Albert, M.J. Blayney, F. Tentori, D.A. Goodkin, R.A. Wolfe, E.W. Young, G.R. Bailie, R.I. Pisoni, and F.K. Port: Rosiglitazone is associated with mortality in chronic hemodialysis patients. *J Am Soc Nephrol* 20(5), 1094-101 (2009)

273. C.A. Schneider, E. Ferrannini r. Defronzo, G. Schernthaner, J. Yates and E. Erdmann: Effect of pioglitazone on cardiovascular outcome in diabetes and chronic kidney disease, *J Am Soc Nephrol* 19(1), 182-7 (2008)

274. Y. Furuse, K. Ogino, M. Shimoyama, N. Sasaki, and I. Hisatome: Ca(2+)-sensitizing effect is involved in the positive inotropic effect of troglitazone. *Br J Pharmacol* 133(8), 1307-13 (2001)

275. P.A. Andrews: Nephrocardiology – a theme for the future? *Br J Diabetes Vasc Dis* 2, 75 (2002)

Key Words: Cardiomyopathy, Chronic Kidney Disease, Insulin Resistance, Metabolism, Treatments, Uraemia, Review

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