Prevalence of Cardiorenal Syndrome in Benha University Hospitals

Thesis

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Internal medicine

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Abbreviations

ADHF	• Acute decompensated heart failure
AKI	• Acute kidney injury
BNP	• brain natriuretic peptide
CHD	• Coronary heart disease
CKD	• Chronic kidney disease
COPD	• Chronic obstructive pulmonary disease
CRS	• Cardiorenal syndrome
ESKD	• End stage kidney disease
GFR	• Glomerular filtration rate
INR	• International normalized ratio
JVP	• Jugular venous pressure

Acknowledgment

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INTRODUCTION

The cardiorenal syndrome is a clinicopathologic disorder in which a primary insult in the kidney or the heart initiates a series of secondary functional and morphological responses in the other organ (**Herzog et al, 2007).**

Cardiorenal syndrome is divided by **Ronco (2008), et al** into five

subtypes:

Type 1: acute cardiorenal syndrome in which acute decompensated heart failure leads to acute kidney injury.

Type 2: chronic cardiorenal syndrome in which chronic heart failure leads to chronic kidney disease.

Type 3: acute renocardiac syndrome in which acute kidney injury leads to acute cardiac dysfunction as arrhythmia or heart failure.

Type 4: chronic renocardiac syndrome in which primary chronic kidney disease contributes to cardiac dysfunction.

Type 5: secondary cardiorenal syndrome in which cardiac and renal dysfunction occurs secondary to a systemic disease such as sepsis or SLE **(Ronco et al., 2008).**

The kidney receives 20% of cardiac output so the heart and the kidney work interdependently so that changes in the volume and pressure in the cardiac atria initiate reflexes that alter the renal function **(Hillege HD et al., 2006).**

Increase in the left atrial pressure is associated with suppression of antidiuretic hormone and arginine vasopressin (Henry

Gauer reflex), this reflex is mediated via the vagus nerve so vagotomy abolishes this reflex, this reflex is responsible for the water diuresis following paroxysmal atrial tachycardia **(Meyer et al, 2008).**

De Bold (1945) observed granules in the cardiac atria when theses granules injected in rats they produced a profound increase in urinary sodium and water, these granules contain a hormone called atrial natriuretic peptide that produces suppression of RAAS system and sympathetic neural activity producing systemic and renal vasodilatation **(Josep et al, 2008).**

The cardiac ventricles contain a similar substance called the brain Natriuretic peptide as it is first found in the brain.

More than 30% of the overall acute decompensated heart failure patients develop renal dysfunction **(Bongartz LG et al, 2005).**

Cardiovascular disease is common in CKD with 43.6% of all, deaths in patients with ESRD due to cardiac cause **(Geisberg et al, 2006)**

Type 1 cardiorenal syndrome acute kidney injury appears to be more severe in patients with decreased left ventricular ejection fraction compaired with normal left ventricular ejection fraction achieving incidence of 70% in patients with cardiogenic shock **(Shale et al, 2006).**

The prevalence Of renal dysfunction in chronic heart failure has been reported to be 25% **(Hostetter et al, 2007).**

Type 3 acute renocardiac syndrome ,the acute kidney injury can produce fluid overload and left sided heart failure, also hyperkalemia can cause arrhythmias and even cardiac arrest,

untreated uraemia and acidosis produces impaired cardiac contractility **(Henry et ah, 2009).**

Type 5 secondary cardiorenal syndrome,severe sepsis is the most common and serious condition affecting both organs **(Haapio et aL, 2008).**

Aim of the work

The aim of this study is to:

1- To assess the prevalence of cardiorenal syndrome in Banha University Hospitals.

2- To study the prevalence of each type of cardiorenal syndrome.

3- To study the prevalence of each type of cardiorenal syndrome in each department in Banha University Hospital.

4- To determine the cause of each type.

5- To study the effect of cardiorenal syndrome on hospital stay and mortality.

Acute Decompensated Heart Failure

Acute decompensated heart failure (ADHF) is the direct cause of approximately one million hospital admissions and contributes to an additional 2.4 million hospitalizations in the United States. It accounts for over 50% of the total annual direct costs for heart failure (HF). (Kozak , et al., 2005).

The in-hospital mortality is in the range of 3% to 4%, and more significantly, the 60- to 90-day mortality rates approach 10%. The burden becomes even more significant when one considers that almost 50% of all patients admitted with this diagnosis are readmitted within 90 days after they are discharged. Although as many as 60% of all patients hospitalized for HF die within 1year, only about 5% to 8% actually die in the hospital. This clearly places the responsibility of HF management in the hands of emergency department (ED) physicians, internists, cardiologists, family practice physicians, and nurses, who rapidly must diagnose and treat the symptoms of HF both acutely and in the long-term outpatient setting. (Francis GS., 2004).

Definition

ADHF refers broadly to new or worsening of signs and symptoms of HF that is progressing rapidly, whereby unscheduled medical care or hospital evaluation is necessary. The mode of presentation of acute HF depends on the etiology and accompanying comorbidities. Common etiologies of ADHF include ischemic cardiomyopathy (60%), hypertension (70%), nonischemic cardiomyopathy, valvular disease, pericardial disease, and acute myocarditis. Typically ADHF is a consequence of impaired left ventricular (LV) function, either systolic or diastolic, with diastolic

dysfunction and hypertension contributing to as much as 50% of all HF-related hospitalizations. Also, about 50% of the patients who have ADHF have reactive hypertension that tends to return to normal within 6 hours of appropriate treatment. Common clinical presentations include ADHF, acute HF accompanying elevation of systemic blood pressure, pulmonary edema, cardiogenic shock with or without low-output syndrome, high-output cardiac failure, and right-sided failure ***(Nieminen , et al.., 2005).***

The management of ADHF is urgent to reduce mortality, decrease length of stay, and avoid need for therapies such as mechanical ventilatory support. The management of ADHF is complicated, however, because many disease processes present with similar symptoms. For example, shortness of breath can be the chief complaint of many other illnesses such as, pneumonia, pulmonary embolism, myocardial infarction, chronic obstructive pulmonary disease (COPD) exacerbation, and asthma. Specifically, differential diagnoses include:

_ Myocardial infarction
_ Congestive HF
_ Pneumonia
_ COPD exacerbation
_ Cardiac tamponade
_ Anxiety
_ Pulmonary embolism
_ Asthma

Making the correct diagnosis is therefore a challenge and selecting the best therapy is even more challenging, requiring a methodical clinical evaluation. ***(Badgett , et al., 1997)***

Clinical evaluation Patients who have ADHF often complain of shortness of breath and other symptoms depending on their hemodynamic status. The clinician must be diligent in gathering a history from the patient and other sources to arrive at the correct diagnosis. Incorporating family members can be helpful in determining how compliant the patient is with

medications and diet, and aid in a more rapid realization of what precipitated the episode of HF. Patients may complain of dyspnea on exertion or at rest, paroxysmal nocturnal dyspnea orthopnea, peripheral edema, fatigue, or cough. In the ADHERE Registry (Acute Decompensated Heart Failure National Registry), which enrolled over 190,000 patient episodes, dyspnea occurred in about 89% of all patients presenting with HF. ***(Fonarow,. 2003)***

Dyspnea on exertion is the most sensitive symptom (negative likelihood ratio .45 with 95% confidence interval [CI], .35 to .67), and paroxysmal nocturnal dyspnea is the most specific (positive likelihood ratio 2.6, 95% CI, 1.5 to 4.5. Peripheral edema was less common, at only 66%. Rapid clinical examination of the patient requires assessment for congestion and signs of low perfusion. Assessment of congestion includes estimation of the jugular venous pressure (JVP) and examination of the lung for crackles. Although the JVP often is evaluated inaccurately, in one study it was found to be the best indicator of ADHF (positive likelihood ratio 5.1, 95% CI, 3.2 to 7.9; negative likelihood ratio 0.66, 95% CI, .57 to .77). ***(Wang , et al.., 2005)***

Jugular venous distention above 10 cm corresponds to a pulmonary capillary wedge pressure of above 22 mm Hg, with an accuracy of 80%. ***(Stevenson , et al.., 1989)***

It must be remembered, however, that the JVP provides closer estimations of right a trial and right ventricular (RV) end–diastolic pressures, and in the absence of lung pathology, provides only a general estimation of left-sided filling pressures. To synthesize the findings of congestion and signs of low perfusion the 2 X 2 table has been recommended (Fig. 1)[9]., in which the clinician can determine in which quadrant the patient currently resides and then select the appropriate therapy. ***(Drazner MH, et al. 2001).***

Most patients presenting with HF are in the right upper quadrant, which is the warm-and- wet sector. This means they have adequate perfusion and are volume overloaded. A few patients who have HF are cold and wet, meaning they are volume over loaded and not perfusing well, as marked by their hypotension. Cold and dry (left lower quadrant) is much more uncommon and is often the result of patients being over diuresed from a group that includes patients who were cold and wet . Patients in the left upper quadrant are not congested and have normal cardiac output and have been admitted to the hospital because of a reason other than HF. A more recent study has emphasized the importance of an elevated JVP and third heart sound in evaluating the prognosis of HF. ***(Chait , et al.., 1972)***

Ancillary evaluation

Several tests may be performed to determine the etiology and support the clinical evaluation of ADHF. Chest radiographs can be obtained quickly, but findings from the ADHERE registry showed that confirmatory evidence of HF occurs in only about 75% of patients. Consistent chest radiograph findings in left side HF is descending order: dilated upper lobe vessels, cardiomegaly, interstitial edema, enlarged pulmonary arteries, pleural effusion, alveolar edema, prominent superior vena cava, and Kerley B lines***. (Peacock ., 2005)***

This means that 25% of all patients presenting with HF have no findings, and one must consider that acute abnormalities may not appear for up to 6 hours after clinical symptoms are present***. (Chakko , et al.., 1991)***

Thus although chest radiographs are helpful, they are not definitive. The presence of interstitial edema on a chest radiograph suggests that the LV end–diastolic pressure or the left atrial pressure is at least 25 mm Hg and increases the likelihood of ADHF about 12-fold. An important caveat is that symptoms and signs (orthopnea, edema, rales, third heart sound and elevated JVP) or radiologic features (cardiomegaly, vascular redistribution,

interstitial or alveolar edema) have a poor predictive value in identifying an elevated LV diastolic pressure greater than 30 mm Hg. ***(Adams KF Jr, et al. 2005)***

An EKG is helpful to detect acute myocardial infarction, ischemia, LV hypertrophy, and arrhythmias. Atrial fibrillation, which is present in about 31% of patients presenting with ADHF or heart block also can contribute to HF symptoms. ***(Fonarow , et al.,. 2005)***

Additionally, pacemaker malfunction can be detected and is becoming more important with the increasing prevalence of cardiac resynchronization therapy. Laboratory evaluation should include a complete blood count, basic metabolic panel, cardiac biomarkers, and international normalized ratio (INR), particularly if the patient is on warfarin. Liver function and thyroid studies should be screened when the situation warrants. The results from some of these tests can lead to useful risk stratification, as recently demonstrated by the classification and regression tree (CART) analysis derived from the ADHERE registry. It showed that a serum urea nitrogen (BUN) of greater than 43 mg/dL was the single best predictor for in hospital mortality, with a systolic blood pressure of less than 115 mm HG being second, and a creatinine of 2.75 mg/dL being third***. (Gheorghiade , et al.., 2007)***

A combination of two or more of these risk factors increases the likelihood of mortality (Fig. 2). Hyponatremia in an HF patient is a sign of failing circulatory homeostasis and is associated with longer length of stay and higher in-hospital and early postdischarge mortality. ***(Gheorghiade , et al. 2007)***

In both OPTIMIZE-CHF, and in Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE).

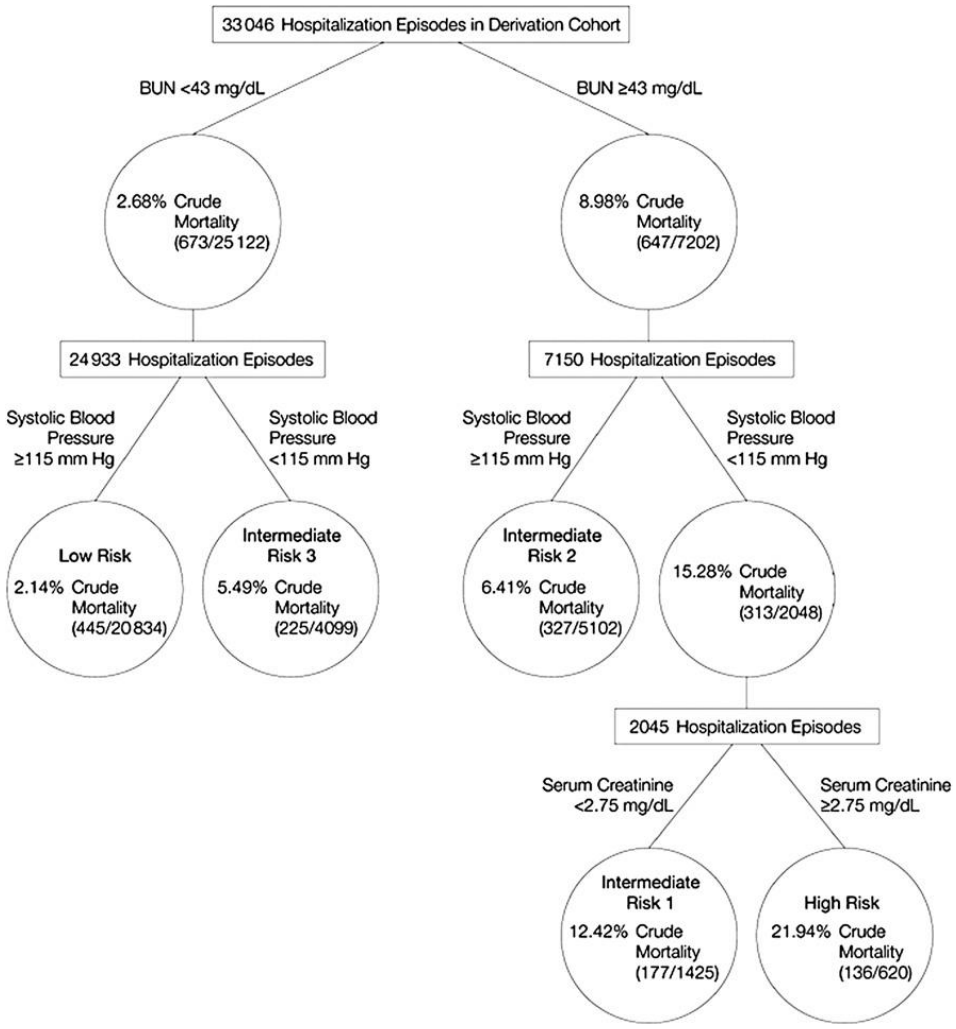


Fig. 2.

Predictors of in-hospital mortality and risk stratification for the derivation cohort. Each node is based on available data from registry patient hospitalizations for each predictive variable presented. Abbreviation: BUN, blood (serum) urea nitrogen. To convert BUN to mmol/L, multiply by 0.357; to convert creatinine to mmol/L, multiply by 88.4. ***(Fonarow GC, et al., 2005)***

25% of patients had hyponatremia on admission and discharge. Tolvaptan has been shown to ameliorate hyponatremia, but it does not improve long term mortality. ***(Konstam , et al.., 2007)***

B-type natriuretic peptide (BNP): At least three types of natriuretic peptides have been identified, with the B type being the only one commercially available for testing. The release of the B-type natriuretic peptide is from ventricular stretch or volume overload and can aid in the

diagnosis of HF. In patients not experiencing HF, BNP levels averaged 38 pg/mL compared with those with HF, whose average was 1076 pg/mL. ***(Harrison A, et al. 2002)***

BNP levels also can be used to risk stratify patients for future events. When patients presented to an ED with a BNP greater than 480 pg/mL, their likelihood of death or HR rehospitalization within 6 months was almost 40%, as compared with a level of 230 pg/mL, in which the likelihood was only 3%. ***(Corteville , et al.., 2007)***

In patients who had stable coronary heart disease (CHD) and no history of heart failure, NT-proBNP levels lower than 100 pg/mL effectively rule out ventricular dysfunction, with a negative likelihood ratio of 0.***28 (Maisel ., 2002)***

So far two forms of testing for this peptide are available in the form of BNP and NT pro-BNP, which is the precursor form. Only BNP has point-of care capability at this time, but both show great promise in helping determine the presence or absence of HF. The diagnosis of HF should not be made with BNP or NT pro-BNP alone, but should be used in conjunction with history, physical examination, chest radiograph, echocardiography, other laboratory tests, and EKG. Special consideration should be made, because conditions exist in which BNP levels can be affected. The levels may be increased with age, female sex, and decreased renal function. ***(Moe , et al.., 2007)***

Morbid obesity has the potential to decrease the level of BNP, making it appear low compared with the true hemodynamic status. Among the greatest values of BNP are its negative predictive value of 89% (95% CI, 87% to 91% when the results are low, less than 100 pg/mL) and the ability to use it as a bedside test to rule in or rule out HF. Among the frustrating aspects of this test are the midrange values between 100 pg/mL and 500 pg/mL in which the diagnosis of HF may be present. This is when

clinical acumen and further testing may be necessary. A chart is provided to help clinicians navigate through the numerous causes of dyspnea and how BNP can help (Fig. 3). ***(Horwich , et al.., 2003)***

An elevated BNP, together with elevated troponins (an indicator of myocardial necrosis), is reported to be associated with a 12-fold increase in mortality, and serial measurements of both biomarkers can add substantially to risk assessment. ***(Moe , et al.., 2007)***

The results from the IMPROVE-CHF study indicate that N-terminal pro-B type natriuretic peptide testing also improves the management of patients who have suspected acute HF. Echocardiography is extremely useful in determining LV ejection fraction, volume, and dimensions, wall motion abnormalities, valvular function, and the presence or absence of endocarditis is invaluable. Any patient who has newly diagnosed HF should have an echocardiogram performed as part of his or her initial work-up. The Joint Commission recommends assessment of LV systolic function in all patients who have suspected HF. ***(Huang , et al.., 2006)***

With the widespread availability of tissue Doppler, it is possible to obtain an estimate of the LV end–diastolic pressure by determining the E:E ratio. When the diagnosis of ADHF is in doubt a markedly elevated E:E' ratio suggests elevated LV end–diastolic pressure. ***(Heidenreich , et al.., 2005)***

To improve prescription of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, it has been suggested that reminders be attached to echocardiograms reporting impaired LV systolic function. ***(Stevenson ., 2006)***

Hemodynamic monitoring The role of the flow-directed thermodilution pulmonary artery catheter (Swan-Ganz catheter) for managing patients who have not responded to initial management and are hypotensive, in shock or a preshock state, has been shown to be of value in experienced centers. This type of monitoring rarely is needed in the routine management of ADHF. ***(Mavric , et al.., 1991)***

When indicated, hemodynamic monitoring can help guide pharmacologic and nonpharmacologic therapy and if there is a need for mechanical support or other interventions. The parameters of greatest interest include: cardiac output, pulmonary capillary wedge pressure, systemic arterial pressure, heart rate, and the calculated systemic vascular resistance (SVR, mean arterial pressure minus mean right atrial pressure, divided by cardiac output). It is important to recognize that metabolic demand may vary significantly among patients; some individuals are able to tolerate a much lower cardiac output, so attention to perfusion, urine output, and mental status must be followed closely. The role of lactate in managing critically ill patients is becoming more important and should be considered in this circumstance. ***(Rosenberg, et al.., 2001)***

Hemodynamic monitoring in HF has come under close scrutiny, and its alue has been questioned, especially after the advent of the ESCAPE trial. This study showed no significant differences in 30-day mortality or clinical utcomes or adverse events at 6 months between patients who received Swan-Ganz catheter and those who did not, begging the question whether his form of monitoring has utility. ***(Mavric , et al.., 1991)***

Although invasive hemodynamic monitoring is not ideal, noninvasive hemodynamic monitoring such as tissue Doppler, or thoracic bioimpedance should continue to play a role in guiding management. In the ESCAPE trial, lower pulmonary capillary wedge pressures achieved during

therapy independently predicted lower 6-month event rates. ***(Mavric , et al.., 1991)***

Treatment

Diuretics have long been a mainstay of HF treatment. Oral diuretics are postulated to lose their effectiveness because of bowel wall edema, which prevents proper gastrointestinal absorption. Therefore the intravenous form of loop diuretics is indicated, because it reduces congestive symptoms through the reduction of volume overload, reduction of mesenteric edema, and improving perfusion across renal vascular beds by means of a decrease in venous pressures without dropping arterial pressure. ***(Packer , et al.., 1999)***

Because no improvement in mortality has been shown with the use of furosemide, it is not indicated as monotherapy for heart failure. ***(Iyengar , et al.., 2007)***

Some form of renal impairment can occur because of increasingly higher doses of oral diuretics. Studies have shown that intravenous furosemide can decrease glomerular filtration rate. ***(Ahmed , et al.., 2006)***

Diuretics are considered standard care for managing HF, largely based on clinical and anecdotal experience. Because of this widespread acceptance, it is unlikely a large multicenter randomized trial ever will be conducted. Important questions, however, remain, including optimal dosage, route of administration, and potential long-term adverse effects, and are worthy of further investigation. ***(Lopez , et al.., 2004)***

The ADHERE study reported that 89% of patients presented with symptoms of volume overload; 88% received intravenous diuretics. Despite this, only 50% of patients were asymptomatic at the time of discharge, and 51% had little or no weight loss (less than 5 lbs) during their hospitalization. This report suggests that too many patients are being discharged rematurely. The IMPACT-HF study found that 60% of patients are being discharged with continuing symptoms of fatigue or dyspnea,

resulting in a 25% rehospitalization rate with in 60 days after discharge. ***(Costanzo , et al.., 2007)***

Although diuretics seem to be helpful in patients who have HF. Wuerz and Meador. showed that when patients experiencing dyspnea were given diuretics in the absence of HF, they had increased mortality. This emphasizes that diuretics are not benign and under scores the importance of making the correct diagnosis and providing proper treatment. Among promising agents are A1-adenosine antagonists, which have shown to increase sodium excretion without causing hypokalemia or azotemia, but large randomized trials of efficacy and safety are needed. ***(Elkayam , et al.., 2004)***

Vasodilators

Vasodilators are important for managing HF due to the hyperadrenergic state and the activation of the renin-angiotensin-aldosterone axis. The most common three agents are nitroglycerin, nitroprusside, and nesiritide. They are not recommended when patients are hypotensive. If a patient becomes hypotensive after a vasodilator has been administered, the clinician should consider the presence of aortic stenosis, volume depletion, RV infarct, or excessive dosing of the drug. ***(Ahmed , et al.., 2006)***

Nitroglycerin

Nitroglycerin's effects are mediated through the relaxation of vascular smooth muscle, and it reduces preload and after load. It can be given orally, topically, or intravenously, as long as blood pressure is maintained. The oral/sublingual form is fast- acting and is given in form that is 10 times greater than the intravenous form, 0.4 mg, versus the starting intravenous dose of 2mg/kg/min. The coronary artery dilation is thought to help with coronary artery perfusion and decrease ischemia. ***(Abraham WT, et al. 2005)***

The dosing of nitroglycerin is often suboptimal and may need to reach doses of about 160mg/kg/min to achieve measurable decreases in pulmonary capillary wedge pressure***. (HasenfussG, et al. 1989)***

Headache is a common adverse effect but is generally ameliorated with acetaminophen, while tachyphylaxis poses a more difficult management issue. Tachyphylaxis is the tolerance level the body develops to a medication. Therefore the body needs increasing amounts to achieve the desired affects. The clinician is left titrating the medication in higher doses and in an unpredictable fashion.

Nitroprusside

Nitroprusside is very effective in reducing preload and afterload. It should be started at doses of .3mg/kg/min and titrated every 5 to 10 minutes according to the change in blood pressure. It no longer is used frequently in HF because of its adverse effect profile and cumbersome requirements for administration. Nitroprusside often requires arterial line monitoring. Its theoretical coronary steal effect, where arteriolar dilation in nonischemic areas shunts blood from areas of ischemia, and accompanying thiocyanate toxicity make it less desirable for managing ADHF. ***(Colucci , et al.., 2000)***

Nesiritide

Nesiritide is identical to the endogenous BNP produced by the body. It acts as a vasodilator on veins and arteries and has some effect on increasing coronary blood flow. antagonizing the renin-angiotensin-aldosterone system and dampening the sympathetic nervous system cause its vasodilator effects. Its starting dose is 2mg/kg bolus, then infusion of .01mg/kg/min. Although nesiritide is more expensive, its use has been accompanied by clinical improvement in symptoms, greater decreases in pulmonary capillary wedge pressures, and less dyspnea at 24 hours than

nitroglycerin. It has a similar effect profile as nitroglycerin except with headache, in which case it is less frequent. The occurrence of symptomatic hypotension in the first 3 hours is about 0.5% . ***(Abraham , et al.., 2005)***

Its use also has been associated with shorter ICU and hospital stays and improvements in heart failure outcomes. Analysis of the ADHERE reported the inpatient survival equivalence between nitroglycerin and nesiritide and increased risk of mortality in patients requiring inotropes. ***(Sackner-Bernstein , et al.., 2007)***

Recent pooled analyses have raised concerns about nesiritide being linked to decreasing renal function and mortality, resulting in a rapid decline in its use in the United States. ***(Yancy , et al.., 2007)***

These studies have been criticized for not controlling qualitative heterogeneity among patient cohorts and the inability to control for baseline inotrope use. More recent data have shown favorable safety, but reports of larger studies that are underway, such as the ASCEND-HF, NAPA, FUSION-II, and BRain NatrIuretic Peptide Versus he Clinical CongesTion ScorE (STARBRITE) trials, will be needed to definitively answer these questions***. (Yancy , et al.., 2004)***

Inotropes

Inotropes are useful for low-output failure and their role is limited in patients who have normal LV systolic function. The adverse effects of arrhythmias, myocardial infarction, and adverse LV remodeling narrow their therapeutic window to one of bridging until a more definitive therapy can be used. Inotropes improve cardiac output and renal blood flow. Dobutamine Dobutamine may be employed when hypoperfusion is present with HF. ***(Elkayam , et al.., 2007)***

It is a catecholamine that has inotropic properties. It is used best to treat pulmonary congestion and low cardiac output. It is a racemic mixture of levo and dextroisomers of potent beta and alpha adrenergic agonists. Dobutamine's mechanism of action is through stimulation of the myocardial beta-1 and to some extent the alpha-1 receptors, which are balanced by opposing alpha-1 and beta-2 stimulation, resulting in minimal vascular resistance, but producing positive inotropic effects. Dobutamine should be used with caution in patients where myocardial ischemia may be present. The effects of dobutamine can increase myocardial oxygen consumption and make ischemia worse, while other properties of the drug actually improve myocardial perfusion in proportion to the increase in oxygen consumption. ***(Elkayam , et al.., 2007)***

Ideally, the drug should be monitored carefully, and when a heart rate increase above 10% of baseline occurs, many clinicians will consider stopping it. Problems in patients who are receiving beta blocker therapy and concurrent dobutamine therapy have been reported and should be considered when difficulties with titration are encountered. In addition, a retrospective analysis suggested increased mortality associated with the use of dobutamine, but it may be useful in selected patients. ***(Leier , 1996)***

Milrinone

Milrinone works by inhibiting the phosphodiesterase III isoenzyme, which leads to increased cyclic adenosine monophosphate (cAMP) and enhanced inotropy. It differs from dobutamine, because it elevates cAMP by preventing its degradation as opposed to dobutamine, which increases cAMP production. Milrinone's effect is achieved by reducing RV and LV filling pressures and increasing cardiac output without significant changes to heart rate and blood pressure. Because it has the potential to decrease blood pressure, it should be used cautiously with hypotension. The pharmacokinetic properties of milrinone make it a less desirable first line agent because of its slow onset and long half-life. ***(Cuffe , et al.., 2002)***

It is for this reason that hypotension can become such a problem in the management of a HF patient with milrinone. Milrinone seems to have some advantage over dobutamine in patients on chronic beta-blocker herapy. It acts beyond the beta receptor level, and therefore its inotropic effects should be unchanged. This is an important consideration, in that so many HF patients are on chronic beta-blocker therapy. If the patient who has HF is on milrinone, the beta-blocker dosage can remain the same or slightly decreased depending on the status of the patient. If the inotropic support becomes prolonged, the beta-blocker should be stopped. Serious concerns about the safety and efficacy of milrinone were raised in the OPTIME study, where patients were found to have about the same ortality rates compared with placebo and a greater incidence of arrhythmias. ***(Felker GM, et al.., 2003)***

The typical patient in acute compensated HF does not benefit from vasopressor therapy in most circumstances. This class of agents is indicated only for the support of blood pressure and to maintain organ perfusion when shock exists. The prognosis is very poor when vasopressor therapy is instituted, especially for an extended duration. Therefore, its role in HF should be minimized, except in conditions of extreme hemodynamic instability. ***(Pagani , et al.., 1999)***

Device therapy

In selected cases of ADHF, device therapy may be considered. Indirect unloading and stabilization of the heart can be achieved with intra-aortic balloon pulsation, extracorporeal membrane oxygenation (ECMO), or Tandem Heart. ***(Chandra , et al.., 2007)***

In emergent cases, mechanical unloading of the heart has been used as rescue therapy. The strengths and limitations of each device need to be known, and cardiologists will have to work closely with cardiothoracic surgeons to determine the best device and most appropriate patients. ***(Costanzo , et al.., 2007)***

Ultrafiltration

Ultrafiltration has emerged as a new therapy to assist in patients who are volume-overloaded and have some element of diuretic resistance. The mechanism of action is to draw fluid off through hydrostatic pressures across a semipermeable membrane. The advantages to this process are small swings in electrolyte balance, while a large volume of fluid can be pulled off. The patient also seems to experience fewer hemodynamic imbalances compared with hemodialysis, even when taking off up to 500 mL per hour. The recent advent of using peripheral venous access has made this modality a possibility in several clinical settings. ***(Hunt ., 2005)***

Long-term treatment

ACE inhibitors have been shown to decrease mortality and hospitalizations. It is recommended that all patients with HF be on an ACE inhibitor before hospital discharge unless there is a contraindication. A decrease of 31% in mortality was shown for patients receiving enalapril who had class IV HF, and a decrease of 16% was shown for patients who had class II and class III HF. ***(Sculpher , et al.., 2000)***

Although the role of ACE inhibitors for managing chronic HF is established, their role in ADHF remains unclear. The adverse effects of ACE inhibitors can include angioedema, which results from increased bradykinin; anaphylaxis is rare. Cough also is reported as an adverse effect

of ACE inhibitors, but should prompt a clinician to search for other causes such as a upper respiratory tract infection or worsening HF before stopping the ACE inhibitor. In general, the cough will go away within 1 to 2 weeks after stopping the drug. Mild azotemia can be encountered when ACE inhibitors are started, and this is tolerated well by patients; rapid rises in azotemia should prompt a consideration of bilateral renal artery stenosis. Oliguria and serum creatinine levels above 3 mg/dL are also contraindications to the use of ACE inhibitors; avoid starting an ACE inhibitor/angiotensin receptor blocker (ARB) when the patient is intravascularly dry. ***(Pitt , et al.., 2003)***

Patients should be started on low doses and titrated up to target levels. Even lower than target doses have been shown to decrease mortality, although higher doses are more cost-effective. ***(Packer , et al.., 1996)***

It may take several weeks to months to exert the full symptomatic benefit, but ACE inhibitors should be instituted for their long-term effects on LV remodeling and mortality. ARBs block the angiotensin II receptors, thereby reducing LV remodeling, arterial vasoconstriction, and renal damage. They seem to have a more favorable adverse effect profile with less cough and angioedema, but they are reserved for patients who are intolerant to ACE inhibitors. Beta-blocker therapy is effective in reducing sympathetic nervous system activity, symptoms, and mortality in patients who have HF. The hyperadrenergic state of HF, as measured by increases in norepinephrine levels, leads to myocardial hypertrophy, increases in afterload, coronary vasoconstriction, and mortality. Both carvedilol and long-acting metoprolol have been shown to reduce mortality in HF. ***(Effect of metoprolol CR/XL in chronic heart failure. 1999)***

Beta-blockers do not seem to have a role in the acute and or critical care setting, except to decrease heart rate if needed; avoid starting a beta-blocker when the patient is wet. This therapy generally is reserved for stable patients. Patients on beta-blocker therapy offer an interesting challenge during an acute decompensated episode. Withdrawing beta-blocker therapy may cause deterioration in the patient's condition; however, the dose may compromise any tenuous hemodynamics. When dobutamine therapy (a beta-agonist) is being used, beta-blockers may need to be stopped, and in some instances milrinone used instead of dobutamine to help improve the patient's condition. Digoxin inhibits the Na þ K þ ATPase of the myocardial cellular membrane and has been used for years to control ventricular response in atrial fibrillation. Digoxin should be avoided as monotherapy in HF. Levels need to be monitored closely, particularly in the elderly and those who have renal insufficiency. Because digoxin does not improve survival. ***(Pitt , et al.., 1999)***

There is a tendency to avoid using it in HF patients with sinus rhythm. Spironolactone has been shown to decrease mortality in class III and IV HF patients by about 30% . ***(Baliga , et al.., 2006)***

It also has been shown to be beneficial in mild-to-moderate HF. Aldosterone receptor blockade, therefore, should be considered in all patients who have HF. Spironolactone should be avoided in patients who have a creatinine level over 2.5 mg/dL or a potassium level over 5 mEq/L. Postdischarge management As mentioned earlier, although as many as 60% of all patients who are hospitalized for HF die within 1 year, only about 5% to 8% actually die in the hospital. ***(Pitt , et al.., 2003)***

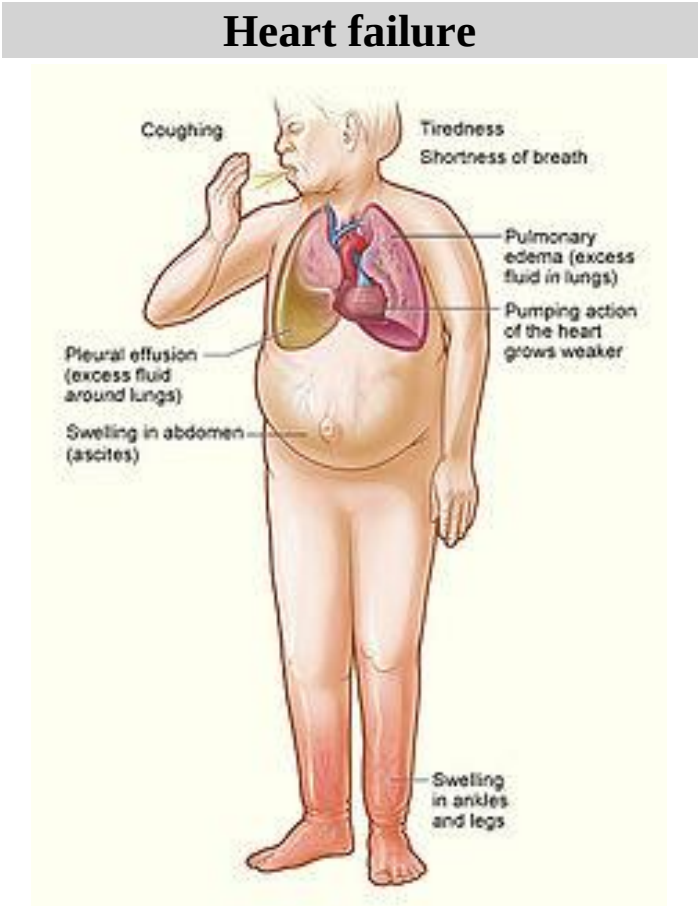
Thirty percent to 50% of recurrent episodes of HF are caused by noncompliance, which also contributes to one third to one half of all

patients readmitted for HF within 6 months of initial hospital discharge. ***(Koelling , et al.., 2005)***

Discharge planning is, therefore, important and should include the prescription of ACE inhibitors and beta-blockers at discharge, and education regarding diet, exercise, compliance with medications, the importance of monitoring daily weights, and smoking cessation. Patients often do not comply with these recommendations because of socio–economic factors and presence of comorbidities including stroke dementia, anemia, diabetes mellitus, hypertension, atrial fibrillation, hyperlipidemia, COPD, and orthostatic hypotension, making a multidisciplinary approach necessary. ***(Inglis , et al.., 2006)***

An approach including the patient as the key member of a team, the HF specialist, a specialist nurse, a pharmacist, a social worker, and a dietician, is required to ensure successful postdischarge management of ADHF. ***(Fonarow , et al.., 2007)***

Chronic Heart Failure



The major signs and symptoms of heart failure

Heart failure (HF), often used to mean chronic heart failure (CHF), occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the needs of the body. The terms congestive heart failure (CHF) or congestive cardiac failure (CCF) are often used interchangeably with chronic heart failure. Signs and symptoms commonly include shortness of breath, excessive tiredness, and leg swelling. The shortness of breath is usually worse with exercise, when lying down, and at night while sleeping. There is often a limitation on the amount of exercise people can perform, even when well treated. ***(McDonagh,et al., 2011)***

Common causes of heart failure include coronary artery disease including a previous myocardial infarction (heart attack), high blood pressure, atrial fibrillation, valvular heart disease, and cardiomyopathy. These cause heart failure by changing either the structure or the functioning of the heart. There are two main types of heart failure: heart failure due to left ventricular dysfunction and heart failure with normal ejection fraction depending on if the ability of the left ventricle to contract is affected, or the heart's ability to relax. The severity of disease is usually graded by how much the ability to exercise is decreased. Heart failure is not the same as myocardial infarction (in which part of the heart muscle dies) or cardiac arrest (in which blood flow stops altogether). Other diseases that may have symptoms similar to heart failure include the following: obesity, kidney problems, liver problems, anemia and thyroid disease among others. ***(McMurray , et al., 2005)***

The condition is diagnosed based on the history of the symptoms and a physical examination with confirmation by echocardiography. Blood tests, electrocardiography, and chest radiography may be useful to determine the underlying cause. Treatment depends on the severity and cause of the disease. In people with chronic disease already in a stable situation, treatment commonly consists of lifestyle measures such as stopping smoking, physical exercise, and dietary changes, as well as medications. In those with heart failure due to left ventricular dysfunction, angiotensin converting enzyme inhibitors and beta blockers are recommended. For those with severe disease, aldosterone antagonists, an angiotensin receptor blocker or hydralazine with a nitrate may be used. ***(National Clinical Guideline for Diagnosis, 2005)***

If there is a normal ejection fraction, associated health problems should be treated. Diuretics are useful for preventing fluid retention and thus recommended. Sometimes, depending on the cause, an implanted device such as a pacemaker or implantable cardiac defibrillator may be useful. A ventricular assist device or occasionally a heart transplant may be recommended in those with severe disease despite all other measures. ***(National Clinical Guideline for Diagnosis, 2010)***

Heart failure is a common, costly, and potentially fatal condition. In developed countries, around 2% of adults have heart failure and in those over the age of 65, this increases to 6–10%. In the year after diagnosis the risk of death is about 35% after which it decreases to below 10% each year. This is similar to the risks with a number of types of cancer. In the United Kingdom the disease is the reason for 5% of emergency hospital admissions. Heart failure has been known since ancient times with the Ebers papyrus commenting on it around 1550 BCE. ***(Taylor, et al., 2014)***

Terminology

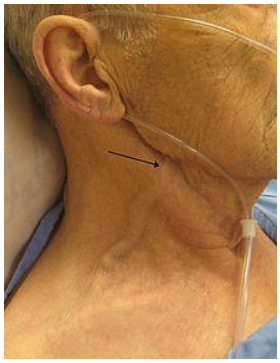
Heart failure is a physiological state in which cardiac output is insufficient to meet the needs of the body and lungs. The termed "congestive heart failure" (CHF) is often used as one of the common symptoms is swelling or water retention. ***(American Heart Association, 2014)***

Heart failure is divided into two different types: heart failure due to reduced ejection fraction (HFREF) also known as heart failure due to left ventricular systolic dysfunction or systolic heart failure and heart failure with preserved ejection fraction (HFPEF) also known as diastolic heart failure or heart failure with normal ejection fraction (HFNEF). Heart failure with reduced ejection fraction occurs when the ejection fraction is less than 40%. In diastolic heart failure, the heart muscle contracts well but the ventricle does not fill with blood well in the relaxation phase. Ejection fraction is the proportion of blood in the heart pumped out of the heart during a single contraction. It is a percentage with normal being between 50 and 75***%. (Heart Rhythm Society, 2014)***

The term "acute" is used to mean rapid onset, and "chronic" refers to long duration. Chronic heart failure is a long term situation, usually with stable treated symptomatology. Acute decompensated heart failure is worsening or decompensated heart failure, referring to episodes in which a

person can be characterized as having a change in heart failure signs and symptoms resulting in death or an urgent need for therapy or hospitalization. Heart failure may also occur in situations of "high output," (termed "high output cardiac failure") where the ventricular systolic function is normal but the heart cannot deal with an important augmentation of blood volume. ***(Jessup , 1977)***

Signs and symptoms



A man with congestive heart failure and marked jugular venous distension. External jugular vein marked by an arrow.

Heart failure symptoms are traditionally and somewhat arbitrarily divided into "left" and "right" sided, recognizing that the left and right ventricles of the heart supply different portions of the circulation. However, heart failure is not exclusively backward failure (in the part of the circulation which drains to the ventricle).

There are several other exceptions to a simple left-right division of heart failure symptoms. Additionally, the most common cause of right-sided heart failure is left-sided heart failure. The result is that patients commonly present with both sets of signs and symptoms. ***(He J; Ogden ; et al., 2001)***

Left-sided failure

Common respiratory signs are increased rate of breathing and increased work of breathing (non-specific signs of respiratory distress). Rales or crackles, heard initially in the lung bases, and when severe, throughout the lung fields suggest the development of pulmonary edema (fluid in the alveoli). Cyanosis which suggests severe hypoxemia, is a late sign of extremely severe pulmonary edema. ***(Baldasseroni ; et al., 2002)***

Additional signs indicating left ventricular failure include a laterally displaced apex beat (which occurs if the heart is enlarged) and a gallop rhythm (additional heart sounds) may be heard as a marker of increased blood flow, or increased intra-cardiac pressure. Heart murmurs may indicate the presence of valvular heart disease, either as a cause (e.g. aortic stenosis) or as a result (e.g. mitral regurgitation) of the heart failure. ***(Fonarow , et al., 2008)***

Backward failure of the left ventricle causes congestion of the lungs' blood vessels, and so the symptoms are predominantly respiratory in nature. Backward failure can be subdivided into failure of the left atrium, the left ventricle or both within the left circuit. The patient will have dyspnea (shortness of breath) on exertion and in severe cases, dyspnea at rest. Increasing breathlessness on lying flat, called orthopnea, occurs. It is often measured in the number of pillows required to lie comfortably, and in orthopnea, the patient may resort to sleeping while sitting up. Another symptom of heart failure is paroxysmal nocturnal dyspnea: a sudden nighttime attack of severe breathlessness, usually several hours after going to sleep. Easy fatigability and exercise intolerance are also common complaints related to respiratory compromise. ***(Nieminen , et al., 2005)***

Right-sided failure

Physical examination may reveal pitting peripheral edema, ascites, and liver enlargement. Jugular venous pressure is frequently assessed as a marker of fluid status, which can be accentuated by eliciting hepatojugular reflux. If the right ventricular pressure is increased, a parasternal heave may be present, signifying the compensatory increase in contraction strength. ***(Collaboration, et al., 2013)***

Backward failure of the right ventricle leads to congestion of systemic capillaries. This generates excess fluid accumulation in the body. This causes swelling under the skin (termed peripheral edema or anasarca) and usually affects the dependent parts of the body first (causing foot and ankle swelling in people who are standing up, and sacral edema in people who are predominantly lying down). Nocturia (frequent nighttime urination) may occur when fluid from the legs is returned to the bloodstream while lying down at night. In progressively severe cases, ascites (fluid accumulation in the abdominal cavity causing swelling) and liver enlargement may develop. Significant liver congestion may result in impaired liver function, and jaundice and even coagulopathy (problems of decreased blood clotting) may occur***. (Boron, et al., 2005)***

Biventricular failure

Dullness of the lung fields to finger percussion and reduced breath sounds at the bases of the lung may suggest the development of a pleural effusion (fluid collection in between the lung and the chest wall). Though it can occur in isolated left- or right-sided heart failure, it is more common in biventricular failure because pleural veins drain into both the systemic and pulmonary venous systems. When unilateral, effusions are often right sided. ***(Shigeyama , et al., 2005)***

Causes

Congestive heart failure

Heart failure may also occur in situations of "high output," (termed "high output cardiac failure") where the ventricular systolic function is normal but the heart cannot deal with an important augmentation of blood volume. This can occur in overload situation (blood or serum infusions), renal diseases, chronic severe anemia, beriberi (vitamin B1/thiamine deficiency), thyrotoxicosis, Paget's disease, arteriovenous fistulae, or arteriovenous malformations. A study of healthy adults in the United States found the following risk factors: ***(Tsutsui , et al., 2007)***

1. Ischemic heart disease 62%
2. Cigarette smoking 16%
3. Hypertension (high blood pressure) 10%
4. Obesity 8%
5. Diabetes 3%
6. Valvular heart disease 2% (much higher in older populations)

Italians had the following underlying causes:

1. Ischemic heart disease 40%
2. Dilated cardiomyopathy 32%
3. Valvular heart disease 12%
4. Hypertension 11%
5. Other 5%

Rarer causes of heart failure include the following:

- Viral myocarditis (an infection of the heart muscle)
- Infiltrations of the muscle such as amyloidosis
- HIV cardiomyopathy (caused by human immunodeficiency virus)
- Connective tissue diseases such as systemic lupus erythematosus
- Abuse of drugs such as alcohol and cocaine
- Pharmaceutical drugs such as chemotherapeutic agents
- Arrhythmias.

Obstructive sleep apnea (a condition of sleep wherein disordered breathing overlaps with obesity, hypertension, and/or diabetes) is regarded as an independent cause of heart failure.

Acute decompensation heart failure

Chronic stable heart failure may easily decompensate. This most commonly results from an intercurrent illness (such as pneumonia), myocardial infarction (a heart attack), arrhythmias, uncontrolled hypertension, or a patient's failure to maintain a fluid restriction, diet, or medication. Other well recognized factors that may worsen CHF include the following: anemia and hyperthyroidism which place additional strain on the heart muscle, excessive fluid or salt intake, and medication that causes fluid retention such as NSAIDs and thiazolidinediones. NSAIDs in general increase the risk twofold. ***(Hunter , et al., 2006)***

Pathophysiology

Heart failure is caused by any condition which reduces the efficiency of the myocardium, or heart muscle, through damage or overloading. As such, it can be caused by a wide number of conditions, including myocardial infarction (in which the heart muscle is starved of oxygen and dies), hypertension (which increases the force of contraction needed to pump blood) and amyloidosis (in which protein is deposited in the heart muscle, causing it to stiffen). Over time these increases in workload will produce changes to the heart itself:

- Reduced force of contraction, due to overloading of the ventricle. In a healthy heart, increased filling of the ventricle results in increased force of contraction (by the Frank–Starling law of the heart) and thus a rise in cardiac output. In heart failure this mechanism fails, as the ventricle is loaded with blood to the point where heart muscle contraction becomes less efficient. This is due to reduced ability to cross-link actin and myosin filaments in over-stretched heart muscle. ***(Dworzynski, et al., 2014)***

- A reduced stroke volume, as a result of a failure of systole, diastole or both. Increased end systolic volume is usually caused by reduced contractility. Decreased end diastolic volume results from impaired ventricular filling – as occurs when the compliance of the ventricle falls (i.e. when the walls stiffen).
- Reduced spare capacity. As the heart works harder to meet normal metabolic demands, the amount cardiac output can increase in times of increased oxygen demand (e.g. exercise) is reduced. This contributes to the exercise intolerance commonly seen in heart failure. This translates to the loss of one's cardiac reserve, or the ability of the heart to work harder during strenuous physical activity. Since the heart has to work harder to meet the normal metabolic demands, it is incapable of meeting the metabolic demands of the body during exercise.
- Increased heart rate, stimulated by increased sympathetic activity in order to maintain cardiac output. Initially, this helps compensate for heart failure by maintaining blood pressure and perfusion, but places further strain on the myocardium, increasing coronary perfusion requirements, which can lead to worsening of ischemic heart disease. Sympathetic activity may also cause potentially fatal arrhythmias. ***(Al Deeb, M; et al., 2014)***
- Hypertrophy (an increase in physical size) of the myocardium, caused by the terminally differentiated heart muscle fibres increasing in size in an attempt to improve contractility. This may contribute to the increased stiffness and decreased ability to relax during diastole.
- Enlargement of the ventricles, contributing to the enlargement and spherical shape of the failing heart. The increase in ventricular volume also causes a reduction in stroke volume due to mechanical and inefficient contraction of the heart. ***(Loscalzo, et al., 2008)***

The general effect is one of reduced cardiac output and increased strain on the heart. This increases the risk of cardiac arrest (specifically due to ventricular dysrhythmias), and reduces blood supply to the rest of the body. In chronic disease the reduced cardiac output causes a number of changes in the rest of the body, some of which are physiological compensations, some of which are part of the disease process:

- Arterial blood pressure falls. This destimulates baroreceptors in the carotid sinus and aortic arch which link to the nucleus tractus solitarii. This center in the brain increases sympathetic activity, releasing catecholamines into the blood stream. Binding to alpha-1 receptors results in systemic arterial vasoconstriction. This helps restore blood pressure but also increases the total peripheral resistance, increasing the workload of the heart. Binding to beta-1 receptors in the myocardium increases the heart rate and makes contractions more forceful in an attempt to increase cardiac output. This also, however, increases the amount of work the heart has to perform. ***(Ewald , et al., 2007)***

- Increased sympathetic stimulation also causes the posterior pituitary to secrete vasopressin (also known as antidiuretic hormone or ADH), which causes fluid retention at the kidneys. This increases the blood volume and blood pressure. ***(Yu, et al., 2014)***

- Reduced perfusion (blood flow) to the kidneys stimulates the release of renin – an enzyme which catalyses the production of the potent vasopressor angiotensin. Angiotensin and its metabolites cause further vasoconstriction, and stimulate increased secretion of the steroid aldosterone from the adrenal glands. This promotes salt and fluid retention at the kidneys. ***(Criteria Committee, et al., 1964)***

- The chronically high levels of circulating neuroendocrine hormones such as catecholamines, renin, angiotensin, and aldosterone affects the myocardium directly, causing structural remodelling of the heart over the long term. Many of these remodelling effects seem to be mediated by transforming growth factor beta (TGF-beta), which is a common downstream target of the signal transduction cascade initiated by catecholamines and angiotensin II, and also by epidermal growth factor (EGF), which is a target of the signaling pathway activated by aldosterone. ***(Raphael , et al., 2007)***

- Reduced perfusion of skeletal muscle causes atrophy of the muscle fibres. This can result in weakness, increased fatigueability and decreased peak strength – all contributing to exercise intolerance. ***(Hunt , et al., 2005)***

The increased peripheral resistance and greater blood volume place further strain on the heart and accelerates the process of damage to the myocardium. Vasoconstriction and fluid retention produce an increased hydrostatic pressure in the capillaries. This shifts the balance of forces in favour of interstitial fluid formation as the increased pressure forces additional fluid out of the blood, into the tissue. This results in edema (fluid build-up) in the tissues. In right-sided heart failure this commonly starts in the ankles where venous pressure is high due to the effects of gravity (although if the patient is bed-ridden, fluid accumulation may begin in the sacral region.) It may also occur in the abdominal cavity, where the fluid build-up is called ascites. In left-sided heart failure edema can occur in the lungs – this is called cardiogenic pulmonary edema. This reduces spare capacity for ventilation, causes stiffening of the lungs and reduces the efficiency of gas exchange by increasing the distance between the air and the blood. The consequences of this are dyspnea (shortness of breath), orthopnea and paroxysmal nocturnal dyspnea. ***(Osama Gusbi, 2002)***

The symptoms of heart failure are largely determined by which side of the heart fails. The left side pumps blood into the systemic circulation, whilst the right side pumps blood into the pulmonary circulation. Whilst left-sided heart failure will reduce cardiac output to the systemic circulation, the initial symptoms often manifest due to effects on the pulmonary circulation. In systolic dysfunction, the ejection fraction is decreased, leaving an abnormally elevated volume of blood in the left ventricle. In diastolic dysfunction, end-diastolic ventricular pressure will be high. This increase in volume or pressure backs up to the left atrium and then to the pulmonary veins. Increased volume or pressure in the

pulmonary veins impairs the normal drainage of the alveoli and favors the flow of fluid from the capillaries to the lung parenchyma, causing pulmonary edema. This impairs gas exchange. Thus, left-sided heart failure often presents with respiratory symptoms: shortness of breath, orthopnea and paroxysmal nocturnal dyspnea. ***(Dickstein , et al., 2008)***

In severe cardiomyopathy, the effects of decreased cardiac output and poor perfusion become more apparent, and patients will manifest with cold and clammy extremities, cyanosis, claudication, generalized weakness, dizziness, and syncope.

The resultant hypoxia caused by pulmonary edema causes vasoconstriction in the pulmonary circulation, which results in pulmonary hypertension. Since the right ventricle generates far lower pressures than the left ventricle (approximately 20 mmHg versus around 120 mmHg, respectively, in the healthy individual) but nonetheless generates cardiac output exactly equal to the left ventricle, this means that a small increase in pulmonary vascular resistance causes a large increase in amount of work the right ventricle must perform. However, the main mechanism by which left-sided heart failure causes right-sided heart failure is actually not well understood. Some theories invoke mechanisms that are mediated by neurohormonal activation. Mechanical effects may also contribute. As the left ventricle distends, the intraventricular septum bows into the right ventricle, decreasing the capacity of the right ventricle. ***(Clinical guideline 108, 2010)***

Systolic dysfunction

Heart failure caused by systolic dysfunction is more readily recognized. It can be simplistically described as failure of the pump function of the heart. It is characterized by a decreased ejection fraction (less than 45%). The strength of ventricular contraction is attenuated and inadequate for creating an adequate stroke volume, resulting in inadequate

cardiac output. In general, this is caused by dysfunction or destruction of cardiac myocytes or their molecular components. In congenital diseases such as Duchenne muscular dystrophy, the molecular structure of individual myocytes is affected. Myocytes and their components can be damaged by inflammation (such as in myocarditis) or by infiltration (such as in amyloidosis). Toxins and pharmacological agents (such as ethanol, cocaine, doxorubicin, and amphetamines) cause intracellular damage and oxidative stress. The most common mechanism of damage is ischemia causing infarction and scar formation. After myocardial infarction, dead myocytes are replaced by scar tissue, deleteriously affecting the function of the myocardium. On echocardiogram, this is manifest by abnormal wall motion (hypokinesia) or absent wall motion (akinesia). ***(Kotecha, et al., 2014)***

Because the ventricle is inadequately emptied, ventricular end-diastolic pressure and volumes increase. This is transmitted to the atrium. On the left side of the heart, the increased pressure is transmitted to the pulmonary vasculature, and the resultant hydrostatic pressure favors extravasation of fluid into the lung parenchyma, causing pulmonary edema. On the right side of the heart, the increased pressure is transmitted to the systemic venous circulation and systemic capillary beds, favoring extravasation of fluid into the tissues of target organs and extremities, resulting in dependent peripheral edema. ***(Liu, et al., 2014)***

Diastolic dysfunction

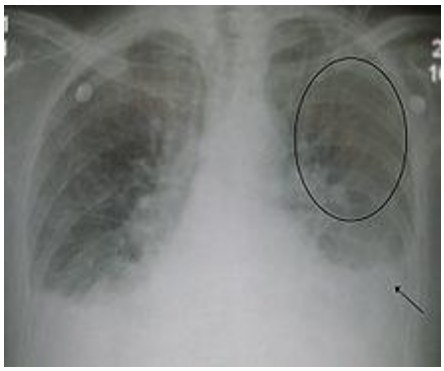
Heart failure caused by diastolic dysfunction is generally described as the failure of the ventricle to adequately relax and typically denotes a stiffer ventricular wall. This causes inadequate filling of the ventricle, and therefore results in an inadequate stroke volume. The failure of ventricular relaxation also results in elevated end-diastolic pressures, and the end result is identical to the case of systolic dysfunction (pulmonary edema in left heart failure, peripheral edema in right heart failure). ***(von Lueder, et al., 2013)***

Diastolic dysfunction can be caused by processes similar to those that cause systolic dysfunction, particularly causes that affect cardiac remodeling.

Diastolic dysfunction may not manifest itself except in physiologic extremes if systolic function is preserved. The patient may be completely asymptomatic at rest. However, they are exquisitely sensitive to increases in heart rate, and sudden bouts of tachycardia (which can be caused simply by physiological responses to exertion, fever, or dehydration, or by pathological tachyarrhythmias such as atrial fibrillation with rapid ventricular response) may result in flash pulmonary edema. Adequate rate control (usually with a pharmacological agent that slows down AV conduction such as a calcium channel blocker or a beta-blocker) is therefore key to preventing decompensation. ***(Faris, et al., 2012)***

Left ventricular diastolic function can be determined through echocardiography by measurement of various parameters such as the E/A ratio (early-to-atrial left ventricular filling ratio), the E (early left ventricular filling) deceleration time, and the isovolumic relaxation time.

Diagnosis



Acute pulmonary edema. Note enlarged heart size, apical vascular redistribution (circle), and small bilateral pleural effusions (arrow).

No system of diagnostic criteria has been agreed on as the gold standard for heart failure. The National Institute for Health and Care Excellence recommends measuring brain natriuretic peptide followed by ultrasound of the heart if positive. ***(Taylor, et al., 2014)***

Imaging

Echocardiography is commonly used to support a clinical diagnosis of heart failure. This modality uses ultrasound to determine the stroke volume (SV, the amount of blood in the heart that exits the ventricles with each beat), the end-diastolic volume (EDV, the total amount of blood at the end of diastole), and the SV in proportion to the EDV, a value known as the ejection fraction (EF). In pediatrics, the shortening fraction is the preferred measure of systolic function. Normally, the EF should be between 50% and 70%; in systolic heart failure, it drops below 40%. Echocardiography can also identify valvular heart disease and assess the state of the pericardium (the connective tissue sac surrounding the heart). Echocardiography may also aid in deciding what treatments will help the patient, such as medication, insertion of an implantable cardioverter-defibrillator or cardiac resynchronization therapy. Echocardiography can also help determine if acute myocardial ischemia is the precipitating cause, and may manifest as regional wall motion abnormalities on echo. ***(He SW, et al., 2009)***

Chest X-rays are frequently used to aid in the diagnosis of CHF. In a person who is compensated, this may show cardiomegaly (visible enlargement of the heart), quantified as the cardiothoracic ratio (proportion of the heart size to the chest). In left ventricular failure, there may be evidence of vascular redistribution ("upper lobe blood diversion" or "cephalization"), Kerley lines, cuffing of the areas around the bronchi, and interstitial edema. Ultrasound of the lung may also be able to detect Kerley lines. ***(Peraira-Moral J. et al., 2012)***

Electrophysiology

An electrocardiogram (ECG/EKG) may be used to identify arrhythmias, ischemic heart disease, right and left ventricular hypertrophy, and presence of conduction delay or abnormalities (e.g. left bundle branch

block). Although these findings are not specific to the diagnosis of heart failure a normal ECG virtually excludes left ventricular systolic dysfunction. ***(Yancy , et al., 2013)***

Blood tests

Blood tests routinely performed include electrolytes (sodium, potassium), measures of renal function, liver function tests, thyroid function tests, a complete blood count, and often C-reactive protein if infection is suspected. An elevated B-type natriuretic peptide (BNP) is a specific test indicative of heart failure. Additionally, BNP can be used to differentiate between causes of dyspnea due to heart failure from other causes of dyspnea. If myocardial infarction is suspected, various cardiac markers may be used. ***(Carrel, et al., 2012)***

According to a meta-analysis comparing BNP and N-terminal pro-BNP (NTproBNP) in the diagnosis of heart failure, BNP is a better indicator for heart failure and left ventricular systolic dysfunction. In groups of symptomatic patients, a diagnostic odds ratio of 27 for BNP compares with a sensitivity of 85% and specificity of 84% in detecting heart failure. ***(Feltner, et al., 2014)***

Angiography

Heart failure may be the result of coronary artery disease, and its prognosis depends in part on the ability of the coronary arteries to supply blood to the myocardium (heart muscle). As a result, coronary catheterization may be used to identify possibilities for revascularisation through percutaneous coronary intervention or bypass surgery. ***(Adler, et al., 2014)***

Monitoring

Various measures are often used to assess the progress of patients being treated for heart failure. These include fluid balance (calculation of fluid intake and excretion), monitoring body weight (which in the shorter term reflects fluid shifts). ***(Auble , et al., 2007)***

Classification

There are many different ways to categorize heart failure, including:

- the side of the heart involved (left heart failure versus right heart failure). Right heart failure compromises pulmonary flow to the lungs. Left heart failure compromises aortic flow to the body and brain. Mixed presentations are common; left heart failure often leads to right heart failure in the longer term.
- whether the abnormality is due to insufficient contraction (systolic dysfunction), or due to insufficient relaxation of the heart (diastolic dysfunction), or to both.
- whether the problem is primarily increased venous back pressure (preload), or failure to supply adequate arterial perfusion (afterload).
- whether the abnormality is due to low cardiac output with high systemic vascular resistance or high cardiac output with low vascular resistance (low-output heart failure vs. high-output heart failure).
- the degree of functional impairment conferred by the abnormality (as reflected in the New York Heart Association Functional Classification)
- the degree of coexisting illness: i.e. heart failure/systemic hypertension, heart failure/pulmonary hypertension, heart failure/diabetes, heart failure/kidney failure, etc. ***(Auble , et al., 2007)***

Functional classification generally relies on the New York Heart Association functional classification. The classes (I-IV) are:

- **Class I**: no limitation is experienced in any activities; there are no symptoms from ordinary activities.
- **Class II**: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.

- **Class III**: marked limitation of any activity; the patient is comfortable only at rest.
- **Class IV**: any physical activity brings on discomfort and symptoms occur at rest. ***(Mehra , et al., 2006)***

This score documents severity of symptoms, and can be used to assess response to treatment. While its use is widespread, the NYHA score is not very reproducible and does not reliably predict the walking distance or exercise tolerance on formal testing. ***(Juenger , et al., 2002)***

In its 2001 guidelines the American College of Cardiology/American Heart Association working group introduced four stages of heart failure:

- Stage A: Patients at high risk for developing HF in the future but no functional or structural heart disorder.
- Stage B: a structural heart disorder but no symptoms at any stage.
- Stage C: previous or current symptoms of heart failure in the context of an underlying structural heart problem, but managed with medical treatment.
- Stage D: advanced disease requiring hospital-based support, a heart transplant or palliative care. ***(Hobbs , et al., 2002)***

The ACC staging system is useful in that Stage A encompasses "pre-heart failure" – a stage where intervention with treatment can presumably prevent progression to overt symptoms. ACC Stage A does not have a corresponding NYHA class. ACC Stage B would correspond to NYHA Class I. ACC Stage C corresponds to NYHA Class II and III, while ACC Stage D overlaps with NYHA Class IV.

Algorithms

There are various algorithms for the diagnosis of heart failure. For example, the algorithm used by the Framingham Heart Study adds together criteria mainly from physical examination. In contrast, the more extensive algorithm by the European Society of Cardiology (ESC) weights the difference between supporting and opposing parameters from the medical

history, physical examination, further medical tests as well as response to therapy. ***(Neubauer ., 2007).***

Framingham criteria

By the Framingham criteria, diagnosis of congestive heart failure (heart failure with impaired pumping capability) requires the simultaneous presence of at least 2 of the following major criteria or 1 major criterion in conjunction with 2 of the following minor criteria: ***(Stewart , et al., 2002)***

Major criteria include the following:

- Cardiomegaly on chest radiography
- S3 gallop (a third heart sound)
- Acute pulmonary edema
- Paroxysmal nocturnal dyspnea
- Crackles on lung auscultation
- Central venous pressure of more than 16 cm H_2O at the right atrium
- Jugular vein distension
- Positive abdominojugular test
- Weight loss of more than 4.5 kg in 5 days in response to treatment (sometimes classified as a minor criterion) ***(Rosamond , et al., 2008)***

Minor criteria include the following:

- Tachycardia of more than 120 beats per minute
- Nocturnal cough
- Dyspnea on ordinary exertion
- Pleural effusion
- Decrease in vital capacity by one third from maximum recorded
- Hepatomegaly
- Bilateral ankle edema

Minor criteria are acceptable only if they can not be attributed to another medical condition such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome. The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure. ***(Rosamond W, et al., 2008)***

ESC algorithm

The ESC algorithm weights the following parameters in establishing the diagnosis of heart failure: ***(Krumholz , et al., 2000)***

Diagnostic assessments supporting the presence of heart failure		
Assessment	Diagnosis of heart failure	
	Supports if	Opposes if normal or
Compatible symptoms	++	++
Compatible signs	++	+
Cardiac dysfunction on	+++	+++
Response of symptoms or signs to	+++	++
ECG		
Normal		++
Abnormal	++	+
Dysrhythmia	+++	+
Laboratory		
Elevated BNP/NT-proBNP	+++	+
Low/normal BNP/NT-proBNP	+	+++
Hyponatraemia	+	+
Renal dysfunction	+	+
Mild elevations of troponin	+	+
Chest X-ray		
Pulmonary congestion	+++	+
Reduced exercise capacity	+++	++
Abnormal pulmonary function	+	+
Abnormal haemodynamics at rest	+++	++
+ = some importance; ++ = intermediate importance; +++ = great		

Differential diagnosis

There are several terms which are closely related to heart failure, and may be the cause of heart failure, but should not be confused with it:

- Cardiac arrest and asystole refer to situations in which there is *no* cardiac output at all. Without urgent treatment these result in sudden death.
- Myocardial infarction ("Heart attack") refers to heart muscle damage due to insufficient blood supply, usually as a result of a blocked coronary artery.
- Cardiomyopathy refers specifically to problems within the heart muscle, and these problems can result in heart failure. Ischemic cardiomyopathy implies that the cause of muscle damage is coronary artery disease. Dilated cardiomyopathy implies that the muscle damage has resulted in enlargement of the heart. Hypertrophic cardiomyopathy involves enlargement and *thickening* of the heart muscle. ***(Bui, ; et al., 2011)***

Management of heart failure

- Treatment focuses on improving the symptoms and preventing the progression of the disease. Reversible causes of the heart failure also need to be addressed (e.g. infection, alcohol ingestion, anemia, thyrotoxicosis, arrhythmia, hypertension). Treatments include lifestyle and pharmacological modalities, and occasionally various forms of device therapy and rarely cardiac transplantation. ***(Bui, ; et al., 2011)***

Acute decompensated heart failure

In acute decompensated heart failure (ADHF), the immediate goal is to re-establish adequate perfusion and oxygen delivery to end organs. This entails ensuring that airway, breathing, and circulation are adequate. Immediate treatments usually involve some combination of vasodilators such as nitroglycerin, diuretics such as furosemide, and possibly non invasive positive pressure ventilation (NIPPV).

Chronic management

The goal of treatment in those with chronic heart failure is the prevention of acute decompensation, to counteract the deleterious effects of cardiac remodeling, and to minimize the symptoms. First-line therapy for all people with heart failure due to reduced systolic function is angiotensin-converting enzyme (ACE) inhibitors. Medicines from this class improve survival and quality of life in those with heart failure. Furthermore, medicines from the beta blocker class have been associated with similar improvement in mortality and symptoms, and are also recommended. The mortality benefits of beta blockers in people with systolic dysfunction who also have atrial fibrillation (AF) is more limited than in those who do not have AF. If the ejection fraction is not diminished (HFPEF), the benefits of beta blockers is more modest; a decrease in mortality has been observed but no reduction in hospital admission for uncontrolled symptoms. ***(Mann , et al., 2012)***

Diuretics have been a mainstay of treatment for treatment of fluid accumulation, and include classes of diuretics such as loop diuretics, thiazide-like diuretic, and potassium-sparing diuretic. Although widely used, evidence on their efficacy and safety is limited. A recent Cochrane review found in a small studies, individuals with heart failure taking diuretics appeared to have improved mortality. However, the extent to which these results can be extrapolated to a general population is unclear due to the small number of participants in the cited studies. (***Goldman, Lee 2011).***

In addition to pharmacologic agents (oral loop diuretics, beta-blockers, ACE inhibitors or angiotensin receptor blockers, vasodilators, and in severe cardiomyopathy aldosterone receptor antagonists), behavioral modification should be pursued, specifically with regard to dietary guidelines regarding fluid intake.

Exercise should be encouraged as tolerated, as sufficient conditioning can significantly improve quality of life and reduce the risk of hospital admission for worsening symptoms. No benefit in mortality has been found for exercise. It is not clear if the evidence can be extended to people with HFPEF, and to when the exercise takes place entirely at home.***(Pfuntner ., et al., 2011)***

Anemia is an independent factor in mortality in people with chronic heart failure; treatment of anemia significantly improves quality of life for those with heart failure, and has been shown to improve the classification of severity of heart failure. Treatment of anaemia improves quality of life and decreases mortality rates. Due to this increasing evidence, the latest European guidelines recommend screening for anaemia and treating with parenteral iron if anaemia is found.***(Elixhauser , et al., 2013)***

In people with severe cardiomyopathy (left ventricular ejection fraction below 35%), implantation of an automatic implantable cardioverter defibrillator (AICD) should be considered to reduce the risk of severe life-threatening arrhythmias. A select population (LVEF <35% and evidence of abnormal conduction on ECG or echocardiogram) will also probably benefit from ventricular resynchronization. In select cases, cardiac transplantation can be considered. While this may resolve the problems associated with heart failure, the person generally must remain on an immunosuppressive regimen to prevent rejection, which has its own significant downsides. Some people with heart failure may also be candidates for ventricular assist devices (VAD), which have commonly been used as a bridge to heart transplants, but are also now being used as treatments for very advanced heart failure in certain people even if transplantation will not be offered. ***(Hines , et al., 2003)***

Palliative care

People with CHF often have significant symptoms, such as shortness of breath and chest pain. Both palliative care and cardiology are trying to get palliative care involved earlier in the course of patients with heart failure, and some would argue any patient with NYHA class III CHF should have a palliative care referral. Palliative care can not only provide symptom management, but also assist with advanced care planning, goals of care in the case of a significant decline, and making sure the patient has a medical power of attorney and discussed his or her wishes with this individual. ***(Strömberg , et al., 2003)***

Without transplantation, heart failure may not be reversible and cardiac function typically deteriorates with time. The growing number of patients with Stage IV heart failure (intractable symptoms of fatigue, shortness of breath or chest pain at rest despite optimal medical therapy) should be considered for palliative care or hospice, according to American College of Cardiology/American Heart Association guidelines. ***(Torio , et al., 2011)***

Prognosis

Prognosis in heart failure can be assessed in multiple ways including clinical prediction rules and cardiopulmonary exercise testing. Clinical prediction rules use a composite of clinical factors such as lab tests and blood pressure to estimate prognosis. Among several clinical prediction rules for prognosing acute heart failure, the 'EFFECT rule' slightly outperformed other rules in stratifying patients and identifying those at low risk of death during hospitalization or within 30 days. Easy methods for identifying low risk patients are: ***(Fisher, et al., 2014)***

- ADHERE Tree rule indicates that patients with blood urea nitrogen < 43 mg/dl and systolic blood pressure at least 115 mm Hg have less than 10% chance of inpatient death or complications.
- BWH rule indicates that patients with systolic blood pressure over 90 mm Hg, respiratory rate of 30 or less breaths per minute, serum sodium over 135 mmol/L, no new ST-T wave changes have less than 10% chance of inpatient death or complications.

A very important method for assessing prognosis in advanced heart failure patients is cardiopulmonary exercise testing (CPX testing). CPX testing is usually required prior to heart transplantation as an indicator of prognosis. Cardiopulmonary exercise testing involves measurement of exhaled oxygen and carbon dioxide during exercise. The peak oxygen consumption (VO2 max) is used as an indicator of prognosis. As a general rule, a VO2 max less than 12–14 cc/kg/min indicates a poor survival and suggests that the patient may be a candidate for a heart transplant. Patients with a VO2 max<10 cc/kg/min have clearly poorer prognosis. The most recent International Society for Heart and Lung Transplantation (ISHLT) guidelines also suggest two other parameters that can be used for evaluation of prognosis in advanced heart failure, the heart failure survival score and the use of a criterion of VE/VCO2 slope > 35 from the CPX test. The heart failure survival score is a score calculated using a combination of clinical predictors and the VO2 max from the cardiopulmonary exercise test. ***(Nowbar, et al., 2014)***

Heart failure is associated with significantly reduced physical and mental health, resulting in a markedly decreased quality of life. With the exception of heart failure caused by reversible conditions, the condition usually worsens with time. Although some people survive many years, progressive disease is associated with an overall annual mortality rate of 10%.

Epidemiology

Heart failure is associated with a high health expenditure, mostly because of the cost of hospitalizations; costs have been estimated to

amount to 2% of the total budget of the National Health Service in the United Kingdom, and more than $35 billion in the United States. ***(Nowbar, et al., 2014)***

Heart failure is the leading cause of hospitalization in people older than 65. In developed countries, the mean age of patients with heart failure is 75 years old. In developing countries, two to three percent of the population have heart failure, but in those 70 to 80 years old, it occurs in 20–30 percent.

More than 20 million people have heart failure worldwide. The prevalence and incidence of heart failure are increasing, mostly because of increasing life span, but also because of increased prevalence of risk factors (hypertension, diabetes, dyslipidemia, and obesity) and improved survival rates from other types of cardiovascular disease (myocardial infarction, valvular disease, and arrhythmias).

In the United States, heart failure affects 5.8 million people, and each year 550,000 new cases are diagnosed. In 2011, congestive heart failure was the most common reason for hospitalization for adults aged 85 years and older, and the second most common for adults aged 65–84 years. Heart failure is much higher in African Americans, Hispanics, Native Americans and recent immigrants from the eastern bloc countries like Russia. This high prevalence in these ethnic minority populations has been linked to high incidence of diabetes and hypertension. In many new immigrants to the U.S., the high prevalence of heart failure has largely been attributed to lack of preventive health care or substandard treatment. Nearly one out of every four patients (24.7%) hospitalized in the U.S. with congestive heart failure are readmitted within 30 days. Additionally, more than 50% of patients seek re-admission within 6 months after treatment and the average duration of hospital stay is 6 days. ***(Nowbar, et al., 2014)***

In tropical countries, the most common cause of HF is valvular heart disease or some type of cardiomyopathy. As underdeveloped countries have become more affluent, there has also been an increase in the

incidence of diabetes, hypertension and obesity, which have in turn raised the incidence of heart failure.

Congestive heart failure is a leading cause of hospital readmissions in the U.S. In a study of 18 States, Medicare patients aged 65 and older were readmitted at a rate of 24.5 per 100 admissions in 2011. In the same year, Medicaid patients were readmitted at a rate of 30.4 per 100 admissions, and uninsured patients were readmitted at a rate of 16.8 per 100 admissions. These are the highest readmission rates for both patient categories. Notably, congestive heart failure was not among the top ten conditions with the most 30-day readmissions among the privately insured ***(Dinicolantonio; et al., 2013)***

Sex

Men have a higher incidence of heart failure, but the overall prevalence rate is similar in both sexes, since women survive longer after the onset of heart failure. Women tend to be older when diagnosed with heart failure (after menopause), they are more likely than men to have diastolic dysfunction, and seem to experience a lower overall quality of life than men after diagnosis.

Economics

In 2011, non-hypertensive congestive heart failure was one of the ten most expensive conditions seen during inpatient hospitalizations in the U.S., with aggregate inpatient hospital costs of more than $10.5 billion. ***(Nowbar, et al., 2014)***

Research

There is low quality evidence that stem cell therapy may help Although this evidence positively indicated benefit, the evidence was of lower quality than other evidence that does not indicate benefit.

A previous claim, which came from a 2012 article published by the British Journal Heart, stated that a low salt diet increased the risk of death in those with congestive heart failure. This claim has since been withdrawn. The paper was retracted by the journal in 2013 because two of

the cited studies contained duplicate data that could not be verified, and the data has since been lost.

Acute kidney injury

Acute kidney injury (formerly known as acute renal failure) is a syndrome characterised by the rapid loss of the kidney's excretory function and is typically diagnosed by the accumulation of end products of nitrogen metabolism (urea and creatinine) or decreased urine output, or both. It is the clinical manifestation of several disorders that affect the kidney acutely. Acute kidney injury is common in hospital patients and very common in critically ill patients. In these patients, it is most often secondary to extrarenal events. How such events cause acute kidney injury is controversial. ***(Alves , et al., 2010)***

No specific therapies have emerged that can attenuate acute kidney injury or expedite recovery; thus, treatment is supportive. New diagnostic techniques (eg, renal biomarkers) might help with early diagnosis. Patients are given renal replacement therapy if acute kidney injury is severe and biochemical or volume-related, or if uraemictoxaemia related complications are of concern. If patients survive their illness and do not have premorbid chronic kidney disease, they typically recover to dialysis independence. However, evidence suggests that patients who have had acute kidney injury are at increased risk of subsequent chronic kidney disease. ***(Appel , et al., 2010)***

Introduction

Acute kidney injury is the new consensus term for acute renal failure. It refers to a clinical syndrome characterised by a rapid (hours to days) decrease in renal excretory function, with the accumulation of products of nitrogen metabolism such as creatinine and urea and other clinically unmeasured waste products. Other common clinical and laboratory manifestations include decreased urine output (not always

present), accumulation of metabolic acids, and increased potassium and phosphate concentrations. ***(Bellomo , et al., 2004)***

The term acute kidney injury has replaced acute renal failure to emphasise that a continuum of kidney injury exists that begins long before sufficient loss of excretory kidney function can be measured with standard laboratory tests. The term also suggests a continuum of prognosis, with increasing mortality associated with even small rises in serum creatinine, and additional increases in mortality as creatinine concentration rises. ***(Hoste , et al., 2006)***

Epidemiology

The described notions have led to a consensus definition of acute kidney injury by the Acute Dialysis Quality Initiative. These RIFLE (risk, injury, failure, loss, end stage) criteria (figure 1) have been broadly supported with minor modifications by the Acute Kidney Injury Network, and both definitions have now been validated in thousands of patients3 and seem to work similarly to each other. A new consensus definition merging the RIFLE criteria and the Acute Kidney Injury Network definition has emerged from the Kidney Disease: Improving Global Outcomes (K-DIGO) group. ***(Mehta , et al., 2007)***

Acute kidney injury is a common and important diagnostic and therapeutic challenge for clinicians. Incidence varies between definitions and populations, from more than 5000 cases per million people per year for non-dialysis-requiring acute kidney injury, to 295 cases per million people per year for dialysisrequiring disease. The disorder has a frequency of 1.9% in hospital inpatients4 and is especially common in critically ill patients, in whom the prevalence of acute kidney injury is greater than 40% at admission to the intensive-care unit if sepsis is present. Occurrence is more than 36% on the day after admission to an intensive-care unit,6 and

prevalence is greater than 60% during intensive-care-unit admission. ***(Hoste , et al., 2006)***

Some causes of acute kidney injury are particularly prevalent in some geographical settings. For example, cases associated with hypovolaemia secondary to diarrhoea are frequent in developing countries, whereas open heart surgery is a common cause in developed countries. Furthermore, within a particular country, specific disorders are common in the community, whereas others arise only in hospitals. Thus, any diagnostic approach to the cause or trigger of acute kidney injury must take into account the local context and epidemiology. ***(Feehally , et al., 2005)***

Key ideas

Most clinicians are familiar with two key ideas related to acute kidney injury namely, acute tubular necrosis and prerenal azotaemia. Acute tubular necrosis describes a form of intrinsic acute kidney injury that results from severe and persistent hypoperfusion of the kidneys (ie, prerenal acute kidney injury), although the term secondary acute kidney injury might be more appropriate. This definition is widely accepted and used in textbooks and by clinicians. However, we have some serious concerns about its use. ***(Macedo , et al., 2009)***

Our first concern is that the term acute tubular necrosis combines a histological diagnosis (tubular necrosis) that is rarely confirmed by biopsy8 and thus is not scientifically verifiable, with a complex clinical syndrome (typically acute kidney injury of >72 h). In many cases, this syndrome has not been convincingly linked with the specific histopathological finding of acute tubular necrosis neither in animals nor in human disease***. (Langenberg , et al., 2008)***

Second, acute tubular necrosis is believed to represent the consequence of sustained or severe prerenal azotaemia, which is not

thought to be associated with histopathological changes (and is therefore not classified as intrinsic acute kidney injury). Such prerenal azotaemia can be expected to resolve in 2–3 days. Unfortunately, the term is conceptually flawed because it implies that clinicians can know with a sufficient degree of certainty that no histopathological injury is present in the tubules by taking a history, examining the patient, and doing urine and blood tests. Such a state is not scientifi cally verifi able unless a renal biopsy sample is taken. Finally, we are concerned that the terms prerenal azotaemia and acute tubular necrosis are biologically flawed because they imply that acute kidney injury does not represent a continuum of injury. For these reasons, such terms are increasingly being challenged. ***(Bellomo , et al., 2007)***

Pathophysiology

The pathogenesis of infl ammatory diseases of the kidney parenchyma (eg, glomerulonephritis and vasculitis) is complex and implicates almost all aspects of the innate inflammatory system and antibody-mediated and immune-cell-mediated mechanisms. In this Seminar, we focus on acute kidney injury secondary to prerenal factors because this form is the most common in developed countries, in hospital inpatients, and particularly in critically ill patients**.** ***(Stoegeman , et al., 2005).***

Much of our understanding of the pathophysiology of prerenal acute kidney injury is derived from work in animals. Studies of models of acute ischaemia induced by acute occlusion of the renal artery show the many pathways that are probably implicated and the mechanisms of organ injury. The coagu lation system is locally activated, leucocytes infi ltrate the kidney, endothelium is injured and adhesion molecules are expressed, cytokines are released, toll-like receptors are induced, intrarenal vasoconstrictor pathways are activated, and apoptosis is induced.

Associated changes also occur in tubular cells with loss or inversion of polarity and loss of adhesion to the basement membrane. Renal injury seems able to trigger organ injury elsewhere (socalled organ cross-talk) through unclear pathways, further emphasising the complexity of the biological response to acute kidney injury. ***(Muirhead N. et al., 2010)***

	GFR criteria	Urine output criteria
Risk	1·5-fold increase in S_{creat} or GFR decrease >25%	UO <0·5 mL/kg/h for 6 h
Injury	Two-fold increase in S_{creat} or GFR decrease >50%	UO <0·5 mL/kg/h for 12 h
Failure	Three-fold increase in S_{creat}, GFR decrease >75%, S_{creat} ≥4 mg/dL, or acute rise in S_{creat} ≥0·5 mg/dL	UO <0·3 mL/kg/h for 24 h or anuria for 12 h
Loss	Complete loss of kidney function >4 weeks	
ESKD	End-stage kidney disease (>3 months)	

Figure 1: **RIFLE criteria for acute kidney injury**
Adapted from Bellomo and colleagues.[1] As GFR or UO deteriorate, the patient moves from risk (class R) to failure (class F). Class R has a high sensitivity and class F a high specificity for acute kidney injury. RIFLE=risk, injury, failure, loss, end stage. GFR=glomerular filtration rate. S_{creat}=serum creatinine concentration. UO=urine output. ESKD=end-stage kidney disease.

Unfortunately, this ischaemic model has little clinical relevance to illnesses such as sepsis. Sepsis is the most common trigger of acute kidney injury in hospital inpatients and in those in the intensive-care unit. The model is also of little relevance to periods of decreased perfusion, as can

happen during major surgery, since 80% renal-artery occlusion for 2 h does not lead to sustained renal dysfunction. ***(Falk RJ, et al., 2010)***

Thus, many of the principles that clinicians use to guide their understanding of acute kidney injury are of questionable relevance to patients in modern hospitals or intensive-care units. In such patients, sepsis, major surgery (especially open heart surgery), and acute decompensated heart failure are the most common triggers of acute kidney injury. The renal artery is not occluded in any of these situations. More relevant models are needed. ***(Saotome T, et al., 2010)***

In view of the uncertainties associated with animal models of acute kidney injury, pursuit of pathogenetic investigations in people seems logical. However, such investigations are diffi cult because taking of renal biopsy samples to investigate acute tubular necrosis is unwarranted in the absence of available therapeutic interventions. Thus, histopathological assessment is used only for rapid post-mortem assessment, which adds major confounders such as selection bias and premortem hypoxia and ischaemia***. (Doi K, Leelahavanichkul A, et al., 2009)***

Despite the development of promising new techniques, assessment of perfusion (ie, renal blood flow) is similarly difficult and confined to invasive techniques. Such data should be interpreted with caution because they show renal blood flow in patients with established acute kidney injury when organ oedema, tubular injury, backleak, and increased tubular luminal pressure could be present and the cause of the measured changes. Reported decreases in renal blood flow could be a result of rather than the cause of, acute kidney injury. Some natural models of human acute kidney injury exist, when injury is expected and the timing of such injury is known—eg, cardiac surgery and renal transplantation. ***(Prowle JR, et al., 2009)***

Cardiac surgery has not yet yielded insights into pathogenesis and does not allow tissue assessment. Renal transplantation has been well studied and allows tissue assessment. However, it is aff ected by the use of nephrotoxic drugs and is an infrequent cause of acute kidney injury. Moreover, we believe that extrapolation of insights gained from a non-perfused, cold-solution-preserved organ outside the body to common clinical triggers of acute kidney injury such as sepsis, bleeding, or major surgery is diffi cult. ***(Prowle JR, et al., 2010)***

Neurohormonal mechanisms

Sympathetic system activation and neurohormonal responses unique to the kidney are activated in acute kidney injury. The renin–angiotensin–aldosterone system, renal sympathetic system, and tubulo glomerular feedback system are activated. Knowledge of these changes has led to schemata of how acute kidney injury can be precipitated in human beings (figure 2). ***(Ramchandra R, et al., 2009)***

These frameworks show that, in situations such as sepsis, infection leads to induction of nitric oxide synthase and nitric-oxide-mediated vasodilation, which in turn causes arterial underfi lling and baroreceptor activation. These circulatory changes trigger activation of the sympathetic system, which induces increased renin–angiotensin–aldosterone activity and renal vasoconstriction. Simultaneously, arginine vasopressin is released and contributes to water retention***.(Schrier RW, et al., 2004)***

These frameworks do not provide information about which particular pathway of injury has primacy in terms of importance or timing, and do not guide the development of new therapeutic interventions. Whether neurohormonal changes lead to intrarenal shunting, or whether such shunting contributes not only to decreased glomerular fi ltration rates, but also to ischaemia of the renal medulla is unknown. Shunting can be coupled with changes in the microcirculation; thus, even if overall renal

blood flow could be measured with reasonable accuracy, under standing of acute kidney injury will remain poor unless the microcirculation is also assessed. ***(Loutzenhiser R, et al., 2010)***

Hepatorenal syndrome is perhaps the most extensively studied form of acute kidney injury in terms of neurohormonal changes, and provides useful mechanistic insights. In this syndrome, as in experimental sepsis, acute kidney injury seems to occur without histopathological renal changes and thus is essentially functional in nature. The intense renal vasoconstriction associated with substantial renin–angiotensin–aldosterone activation is the characteristic finding in patients with hepatorenal syndrome, suggesting that neurohormonal events bring about the development of the disorder. Although the mechanisms that cause such activation are debated, decreased systemic blood pressure secondary to splanchnic vasodilation is judged a key event. ***(Moreau R, et al., 2008)***

The neurohormonal response to such vasodilation supports the systemic circulation, but renal circulation can be adversely aff ected. Whether a similar state occurs in other diseases associated with hypotension and systemic vasodilation (eg, infl ammation and sepsis) remains unknown. Thus, increases in norepinephrine, renin, and angiotensin II concentrations can contribute to other forms of acute kidney injury, suggesting that, at least in some situations, neurohormonal renal vasoconstriction could be a fundamental mechanism of loss of excretory function. ***(Salerno F, et al., 2007)***

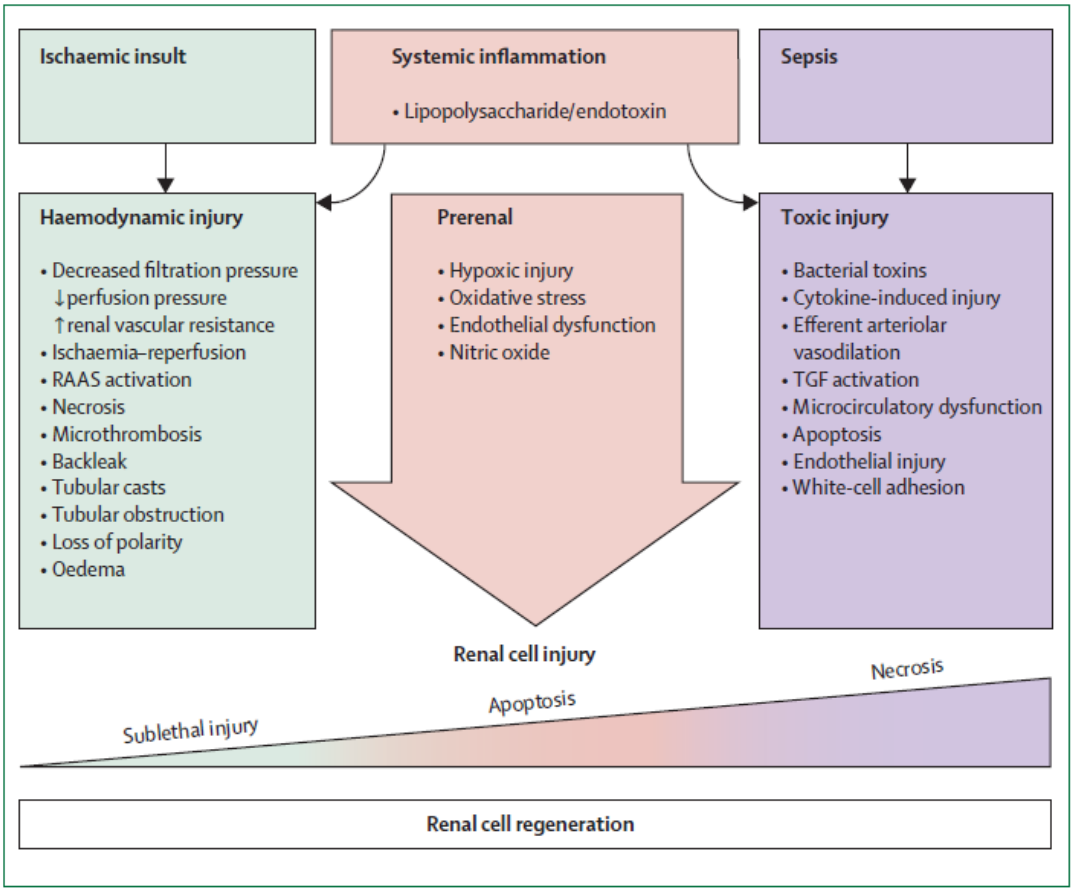


Figure 2: **Key potential pathways implicated in pathogenesis of acute kidney injury due to ischaemia or sepsis**
The timing of activation of each pathway, their interaction, and the hierarchy of these pathways remain unknown. RAAS=renin–angiotensin–aldosterone system. TGF=tubuloglomerular feedback.

Diagnosis

Because acute kidney injury is asymptomatic until extremes of loss of function are reached and has no characteristic clinical fi ndings, diagnosis typically occurs in the context of another acute illness. Although oliguria is a helpful sign, it is neither specifi c nor sensitive. Under most circumstances, acute kidney injury is diagnosed in high-risk contexts (eg, sepsis, major surgery, bleeding, volume losses) by laboratory tests. Creatinine and urea concentrations are the standard diagnostic analytes. ***(Wong F, et al., 2011)***

When a patient presents with raised serum creatinine concentrations, to establish whether the patient has acute kidney injury, chronic kidney disease, or a bout of acute illness superimposed on chronic disease is important. Usually, the clinical context provides clues. Abnormal serum creatinine before presentation; relevant risk factors (eg, hypertension or diabetes); a slow clinical course for the presenting illness; high serum concentrations of creatine or phosphate, or both; and normocytic anaemia all suggest the presence of chronic kidney disease. Renal ultrasonography might show small kidneys and provide evidence of chronic disease. ***(Moreau R, et al., 2008)***

In some cases, acute kidney injury has a sudden and easily identifi able cause (eg, pneumonia with septic shock, cardiac surgery, trauma with haemorrhagic shock, diarrhoea), which makes the presence of obstruction unlikely. In some situations, the presence of substantially increased intra-abdominal pressure as a trigger is easily suspected because of the clinical context and raised bladder pressure. In other situations, however, presentation is less clear and the possibility of obstruction as a cause of acute kidney injury or acute-on-chronic kidney disease should be considered. In any case, renal ultrasonography could be of use. ***(Macedo E, et al., 2011)***

Although most cases of intrinsic acute kidney injury are associated with prerenal triggers and typically thought to be due to acute tubular necrosis, in some patients the illness is secondary to infl ammatory parenchymal disease. Of these cases, diseases such as vasculitis, glomerulo nephritis, and interstitial nephritis are the most common. Clinical features might suggest one of these diagnoses—eg, systemic manifestations in vasculitis, the presence of macroscopic haematuria in glomerulonephritis, or the recent initiation of treatment with a drug known to cause interstitial nephritis. Other common causes of paren chymal acute kidney injury are malignant hyper tension, pyelonephritis, bilateral cortical necrosis, amyloidosis, malignant disease, and nephrotoxins. ***(Platell C, et al., 1990)***

Often, patients present with acute kidney injury in the absence of obstruction or a clear prerenal cause. In such patients, urinary microscopy frequently suggests glomerular pathological changes, with haematuria; proteinuria; or fragmented red cells, red-cell casts, white-cell casts, or granular casts; or any combination of these factors. When interstitial nephropathy is suspected, urine samples should be tested for eosinophils. However, the sensitivity of the test is poor. Urine biochemical analysis is of little use, especially in sepsis. Measurement of variables such as the fractional excretion of sodium or urea has not been consistently shown to have a clear correlation with histopathological fi ndings in systematic reviews of work in animals, or in people. Biochemical investigations have little association with biomarkers of injury, clinical course, or prognosis in critically ill patients. ***(Bagshaw SM, et al., 2010)***

Albuminuria, however, is a strong risk factor for the development of acute kidney injury and a potential biomarker of the disease. The relation between histopathology and urine microscopy (a possible surrogate measure of tubular injury) is unknown. However, the urinary microscopy score (based on the quantifi cation of tubular cells and casts) correlates with biomarkers of injury, worsening acute kidney injury, need for renal replacement therapy, and hospital mortality. The therapeutic implications of any urinary fi ndings are unknown. Blood tests can detect evidence of an unexplained infl ammatory state, and specifi c tests for autoantibodies can show patterns suggestive of specifi c types of vasculitis. If deemed clinically appropriate, a renal biopsy might show diagnostic changes. ***(Bagshaw SM, et al., 2009)***

Nephrotoxic drugs

Drug-induced acute kidney injury is important because the off ending drug can often be identifi ed and removed or substituted for one that is non-nephrotoxic or less nephrotoxic. Additionally, many aff ected patients present with polyuric acute kidney injury, and thus a high index of suspicion is crucial for diagnosis. Drugs seem to contribute to acute kidney injury in roughly 20% of patients, especially in critically ill patients. Panel shows a list of frequently prescribed drugs that are known to contribute to acute kidney injury. For several nephrotoxic drugs (eg, aminoglycosides, angiotensinconverting enzyme inhibit ors, calcineurin inhibitors, non-steroidal anti-infl ammatory drugs) admin istration can be suspended, the pattern of admin istration changed, or another less toxic or non-toxic drug used instead, but this strategy cannot be used for all drugs. ***(Bentley ML, et al., 2010)***

Iodinated radiocontrast agents are a unique and important cause of acute kidney injury because of their use in angiography. Evidence from randomised controlled trials shows that contrast-induced neph ropathy can be lessened by use of iso-osmolar contrast agents and isotonic fluid loading. The use of other protective interventions—eg, N-acetylcysteine—is contro versial. Similar amounts of uncertainty surround the use of bicarbonate and other less extensively studied interventions. ***(Aspelin P, et al., 2003)***

Laboratory assessment of renal function

The laboratory hallmarks of acute kidney injury are increased serum creatinine concentrations or raised plasma urea concentrations, or both. Unfortunately, these waste products are insensitive markers of glomerular filtration rate and are modified by nutrition, use of steroids, presence of gastrointestinal blood, muscle mass, age, sex, muscle injury, and

aggressive fluid resuscitation. Furthermore, they become abnormal only when glomerular filtration rate decreases by more than 50% and do not show dynamic changes in filtration rates. Despite these shortcomings, clinical monitoring remains based on the measurement of urea and creatinine concentrations. The use of sophisticated radionuclide-based tests is cumbersome and useful only for research purposes. However, new biomarkers of renal injury and function are emerging for the diagnosis of acute kidney injury. ***(Brar SS, et al., 2008)***

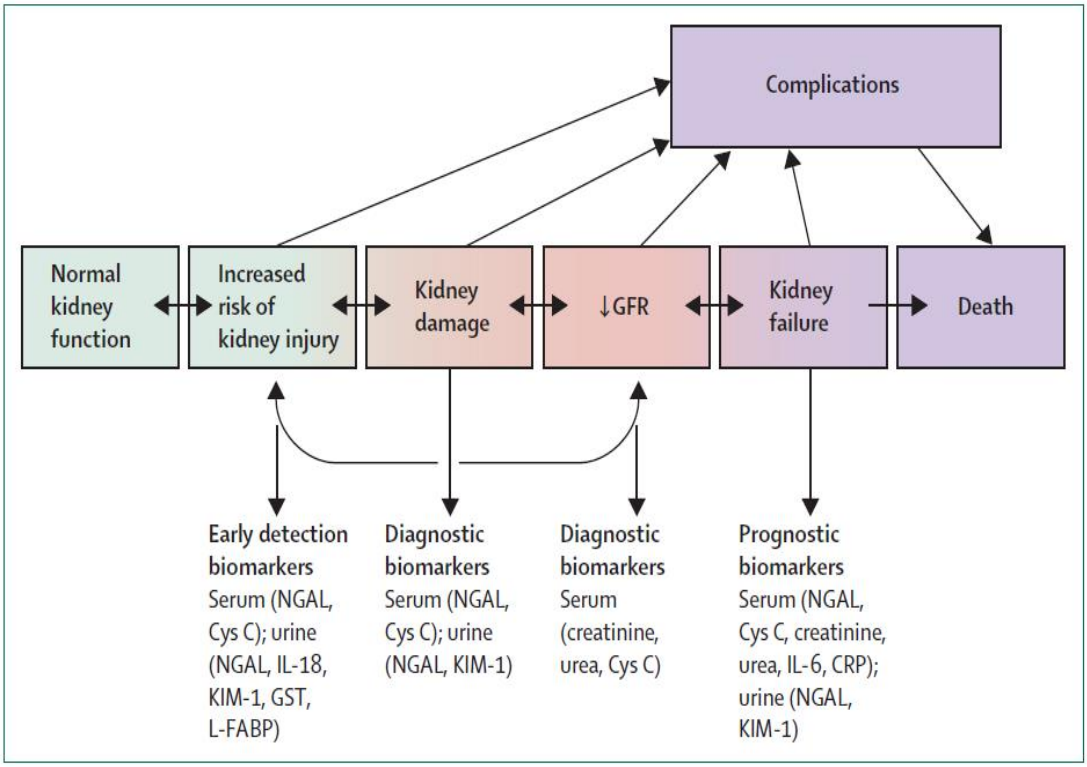


Figure 3: **Evolution of acute kidney injury**
Injury begins before excretory function is lost (ie, decreased GFR) and can in some cases be detected by the measurements of biomarkers. Such biomarkers can also be used for diagnostic and prognostic assessment. GFR=glomerular filtration rate. NGAL=neutrophil gelatinase-associated lipocalin. Cys C=cystain C. KIM-1=kidney injury molecule 1. IL-18=interleukin 18. GST=glutathione-S-transferase. L-FABP=liver fatty-acid-binding protein. CRP=C reactive protein. IL-6=interleukin 6.

Panel 1: **Drugs that contribute to acute kidney injury**

- Radiocontrast agents
- Aminoglycosides
- Amphotericin
- Non-steroidal anti-infl ammatory drugs
- β-lactam antibiotics (specifi cally contribute to interstitial nephropathy)
- Sulphonamides
- Aciclovir
- Methotrexate
- Cisplatin
- Ciclosporin
- Tacrolimus
- Angiotensin-converting-enzyme inhibitors
- Angiotensin-receptor blockers

Some biochemical test results are abnormal in patients with acute kidney injury and such tests are useful to establish whether renal replacement therapy should be started. For example, a high (>6 mmol/L) or rapidly rising potassium concen tration increases the risk of life-threatening arrhythmias and requires both specific potassium-lowering treatment and possible early renal replacement therapy. Similarly, decompensated marked metabolic acidosis with acidae mia should prompt consideration for renal replacement therapy. ***(Masuda M, et al., 2008)***

In specific situations, other investigations are necessary to establish the diagnosis, such as measure ment of creatine kinase and free myoglobin to identify possible rhabdomyolysis. Chest radiographs, blood films, measurement of non-specific inflam matory markers, and assays that detect specifi c antibodies (eg, those against glomerular basement membrane, neutrophil cytoplasm, DNA, or smooth muscle) are useful screening tests to help support the diagnosis of vasculitis, specific types of collagen

disease, or glomerulo nephritis. If thrombotic–thrombocytopenic purpura is suspected, concentrations of lactic dehydro genase, haptoglobin, unconjugated bilirubin, and free haemoglobin should also be measured. The presence of microangiopathic haemolysis in blood smears is also crucial for this diagnosis. In some patients, specifi c fi ndings—eg, cryoglobulins, Bence-Jones pro teins—provide almost conclusive diagnosis. Rarely, clinical signs, laboratory inves tigations, and radiological investi gations are not suffi cient to make a causative diagnosis with certainty. In such patients a renal biopsy might be necessary. ***(Hoste EA, et al., 2010)***

Novel biomarkers

Investigators have used new search techniques based on proteomics to identify several novel biomarkers of acute kidney injury. Despite the novelty and dynamic nature of this new research specialty, several key points can already be made.

First, in patients who develop acute kidney injury, concen trations of these biomarkers seem to change earlier than do serum creatinine concentrations (figure 3). Typically, these biomarkers have been most extensively assessed after cardiac surgery or on presentation to the emergency department. ***(Devarajan P, et al., 2010)***

Second, they seem to show diff erent aspects of renal injury. For example, cystatin C concentrations seem to show changes in glomerular fi ltration rate, whereas concentrations of neutrophil gelatinase-associated lipocalin are related to tubular stress or injury. ***(Haase M, et al., 2011)***

Third, these biomarkers seem to change with treatment or recovery, which suggests that they can be used to monitor interventions. ***(Maisel AS, et al., 2011)***

Fourth, they can identify subpopulations of patients who do not have acute kidney injury according to creatinine-based criteria, but actually have a degree of kidney stress or injury that is associated with worse outcomes***(Haase M, et al., 2009)***

Finally, by identifying possible mechanisms of injury, novel biomarkers increase our understanding of the pathogenesis of acute kidney injury. Although neutrophil gelatinase-associated lipocalin is the most studied renal biomarker, several other biomarkers are under investigation. Whether the additional cost (£5–20 per test) is worthwhile, or whether this research will yield therapeutic benefi ts has not been established***. (Srisawat N, et al., 2011)***

Prevention

The fundamental principle of prevention of acute kidney injury is to treat the cause or trigger. If prerenal factors contribute, they should be identified, haemo dynamic resuscitation quickly begun, and intravascular volume maintained or rapidly restored. In many patients, insertion of a peripheral intravenous catheter and rapid administration of intravenous fluids are suffi cient to complete this process. The choice of fluid for such resuscitation is controversial. In particular, the possibility that fluids containing large-molecular-weight starch are nephro toxic is of concern. Whether fluids containing novel low-molecular-weight starch are also nephrotoxic is the subject of a large double-blind randomised controlled trial in progress ***(NCT00935168). (Dart AB, et al., 2010)***

Central volume status can be monitored by physical examination, neck vein inspection, and measurement of blood pressure and heart rate. However, if the patient is acutely ill, invasive haemodynamic monitoring (eg, central venous catheter, arterial cannula, and cardiac output monitoring in some cases) is often the best assessment. Adequate

oxygenation and haemoglobin concentration (at least 70 g/L) should be maintained or immediately restored. Once intravascular volume has been restored, some patients remain hypotensive (mean arterial pressure <65–70 mm Hg). In such patients, autoregulation of renal blood flow can be lost, contributing to acute kidney injury. Restoration of a higher mean arterial pressure might raise the glomerular fi ltration rate and has no appreciable disadvantage. ***(Liu YL, et al., 2009)***

However, vasopressor drugs might be needed to bring about such increases in mean arterial pressure. The nephroprotective role of additional fluid therapy in a patient with a normal or increased cardiac output and blood pressure is questionable. Despite resuscitation measures, acute kidney injury can still develop if cardiac output is inadequate. Inotropic drugs or the application of ventricular assist devices might be necessary to treat a low cardiac output state. ***(Bagshaw SM, et al., 2007)***

After haemodynamic resuscitation and removal of nephrotoxins, no specific drug-based intervention has been consistently and reproducibly shown to be protective. The alleged nephroprotective effect of socalled renal-dose or low-dose dopamine was refuted by findings from a multicentre, randomised, double-blind placebo-controlled trial. Loop diuretics might protect the loop of Henle from ischaemia by decreasing its transport-related workload. However, no results from double-blind, ran domised controlled studies of suitable size have shown that these agents reduce the incidence of acute kidney injury. The usefulness of diuretics remains confi ned to the control of fluid status. Other drugs such as theophylline, urodilatin, fenoldopam, bicarbonate, and atrial natriuretic peptide have been studied in different subgroups of patients and clinical contexts. However, such studies have been negative, too small, single centre, confined to a very specific group of patients, or have not yet been reproduced. Thus, no established pharmacotherapy exists for acute kidney injury. ***(Lin J, Bonventre JV., et al., 2005)***

Management of established disease

General management

The principles of management of established acute kidney injury are to treat or remove the cause and to maintain homoeostasis while recovery takes place. Complications can be prevented in some cases by actions that vary in complexity from fluid restriction to extracorporeal renal replacement therapy. Most experts recommend that nutritional support should be started early, contain adequate calories and protein, and be given as for other hospital inpatients or those in intensive-care units. No evidence shows that specific renal nutritional solutions are useful or necessary. The recommended daily allowance of vitamins and trace elements should be given. The enteral route is preferred to the use of parenteral nutrition. Patients with hyperkalaemia (potassium concentrations >6 mmol/L) should be promptly given insulin and dextrose, a bicarbonate infusion (if acidosis is present), or nebulised salbutamol, or all three. If the serum potassium concen tration is higher than 7 mmol/L or electrocardiographic signs of hyperkalaemia are present, 10 mL of 10% calcium gluconate solution should also be given intravenously. ***(Bellomo R, et al., 2005)***

These treatments are temporising actions while renal replacement therapy is set up. Metabolic acidosis is almost always present but rarely requires treatment perse (unless severe). Anaemia might need correction.

Drug therapy should be adjusted to take into account the decreased clearance associated with loss of renal function. Stress-ulcer prophylaxis is advisable. Careful attention should be paid to the prevention of infection. Fluid overload can sometimes be prevented by the use of loop diuretics in patients with polyuria. No specific recommendations exist for the management of fluids, and fluid restriction might be appropriate in some patients. However, we believe that the best way to avoid fluid overload in fluid-resuscitated critically ill patients with pronounced oliguria or anuria is to institute renal replacement therapy at an early stage. We recommend this strategy because some fluid overload already exists, and nutritional intake typically requires at least 1L of fluid per day and drug intake

another 500 mL per day. These fluid sources cannot be compensated for by insensible losses. The importance of fluid overload as a major contributor to increased risk of death in patients with acute kidney injury is increasingly recognised. ***(Lewis J, et al., 2000)***

10–20% overload can be suffi cient to cause adverse clinical consequences. Substantial azotaemia (suggested by urea concentrations >30 mmol/L or creatinine concentrations >300 μmol/L) is judged a marker of an undesirable toxic state. However, no recommendations state the severity of acute azotaemia that can be tolerated. We believe that this degree of azotaemia should probably be treated with renal replacement therapy unless recovery is imminent or already underway, or unless a return towards normal urea and creatinine concentrations is expected within 24–48 h. However, no randomised controlled trials have defined the ideal time for intervention with artifi cial renal support. ***(Fiaccadori E, et al., 2008)***

Hepatorenal syndrome

Hepatorenal syndrome is a form of acute kidney injury that arises in patients with severe liver dysfunction. Typically, patients present with progressive oliguria with a low urinary sodium concentration (<10 mmol/L). However, in patients with severe liver disease, other causes of acute kidney injury are much more common than is hepatorenal syndrome—eg, sepsis, paracentesisinduced hypovolaemia, diuretic-induced hypovolaemia, lactulose-induced hypovolaemia, cardiomyopathy, or any combination of these factors. Treatment of the trigger of deterioration and avoidance of hypovolaemia (preferably by albumin administration) can help to decrease the incidence of acute kidney injury. Notably, findings from several studies suggest that the long-acting vasopressin derivative terlipressin can improve glom erular filtration rates and perhaps patient outcomes, and this drug is becoming widely used. ***(Prowle JR, et al., 2010)***

Rhabdomyolysis

Rhabdomyolysis-associated acute kidney injury accounts for roughly 5–10% of cases of the disorder in intensivecare units, dependent on the setting. Prerenal, renal, and postrenal factors are implicated in its pathogenesis. Rhabdomyolysis-associated acute kidney injury is typically seen after major trauma, narcotics overdose, vascular embolism, or use of drugs that can induce major muscle injury. The principles of treatment are based on retrospective data, small series, and multivariate logistic regression analysis because no randomised controlled trials have been done. These principles include prompt and aggressive fluid resuscitation, elimination of causative drugs, correction of compartment syndrome, alkalinisation of urine (pH >6 · 5), and maintenance of polyuria (>300 mL/h). Typically, rhabdomyolysis is an issue of concern in scenarios such as mass disasters—eg, earthquakes or explosions. In such settings, the deployment of renal-protection and disaster teams with appropriate portable dialysis facilities can make a big diff erence to outcomes. ***(Ortega R, et al., 2002)***

Cardiorenal syndrome

The changing demographics of patients in developed countries and the rising incidence of chronic heart failure and chronic kidney disease have led to an increase in patients with both heart disease and acute kidney injury. Acute kidney injury is often super imposed on chronic kidney disease and is frequently triggered by an acute decompensation of heart failure. A growing amount of published work focuses on so-called cardiorenal syndromes. Although such investigations are quite new, initial insights are emerging—eg, the notion that a congestive state might contribute more to the pathogenesis of acute kidney injury than might low blood pressure and cardiac output***.(Sagi SV, et al., 2010)***

Panel 2: **Conventional criteria for initiation of renal replacement therapy in acute kidney injury**

1- Anuria (negligible urine output for 6 h)
2- Severe oliguria (urine output <200 mL over 12 h)
3- Hyperkalaemia (potassium concentration >6.5 mmol/L)
4- Severe metabolic acidosis (pH <7.2 despite normal or low partial pressure of carbon dioxide in arterial blood)
5- Volume overload (especially pulmonary oedema unresponsive to diuretics)
6- Pronounced azotaemia (urea concentrations >30 mmol/L or creatinine concentrations >300 μmol/L)
7- Clinical complications of uraemia (eg, encephalopathy, pericarditis, neuropathy)*

*Complications of uraemia should be prevented by avoidance of unnecessarily high degrees of azotaemia.

Renal replacement therapy

In some patients, acute kidney injury is severe enough to require renal replacement therapy. No one set of criteria exists to guide such intervention. However, when clinicians make this decision, they consider factors such as potassium, creatinine, and urea concentrations; fluid status; acid–base status; urine output; the overall course of the patient's illness; and the presence of other complications (panel 2).

The best time to start renal replacement therapy is controversial because the only studies linking timing with outcome are observational. Three forms of renal replacement therapy are available: continuous, intermittent (either as intermittent haemodialysis or slow lowefficiency dialysis), and peritoneal dialysis. Continuous renal replacement therapy can involve fi ltration alone (eg, continuous venous–venous haemo filtration) or diffusion alone (eg, continuous veno–venous haemo dialysis), or both (eg, continuous veno–venous haemo diafiltration). ***(Bagshaw SM, et al., 2009)***

Peritoneal dialysis is associated with clearance limitations and diffi culties with fluid removal (and potential complications), and is thus rarely used in adults in developed countries. Should intermittent renal replacement therapy or continuous renal replacement therapy be used? No suitably powered randomised controlled trials have been done to address this question. However, results of small-to-medium-sized studies do not

suggest a difference in patient survival. Thus, on the basis of patient survival, intermittent haemodialysis, slow lowefficiency dialysis, and continuous renal replacement therapy all seem to be acceptable options.***(Bagshaw SM, et al., 2008)***

The appropriate intensity of renal replacement therapy is uncertain, especially in critically ill patients, who most often need this treatment. A single-centre medium-sized study suggested that an increase of continuous renal replacement therapy from 20 mL/kg/h of effl uent generation to greater than 35 mL/kg/h might be associated with increased survival. In response to this finding, two large multicentre randomised controlled studies were designed: the Acute Renal Failure Trial Network (ATN) study and the Randomised Evaluation of Normal versus Augmented Level of Renal Replacement Trial ***(RENAL) study.(Ronco C, et al., 2000)***

Both showed no difference in survival rates with increasing intensity of renal replacement therapy. These findings suggest that the prescribed dose of renal replacement therapy should be equivalent to 25–30 mL/kg/h, to take into account the effect of down time, and that a plateau in effectiveness is apparent at such doses. Moreover, nearly all patients with acute kidney injury who were on vasopressor support received continuous renal replacement therapy in the ATN and REAL trials. Thus, by practice consensus, continuous renal replacement therapy was treated as the de-facto standard of care in haemo dynamically unstable patients in both trials. ***(Bell M; et al., 2007)***

Renal recovery was much greater in the RENAL trial (with almost exclusive use of continuous renal replacement therapy) than in the ATN trial (with substantial use of intermittent haemodialysis), suggesting that continuous therapy might help with renal recovery. Therefore the cost-effectiveness of such therapies should be judged on the basis of their possible effect on recovery. In critically ill patients, the cost difference is small in the context of daily care and is dependent on region or institution. ***(Uchino S, et al., 2007)***

If continuous renal replacement therapy is given, anticoagulation of the circuit might be necessary. Either low-dose heparin (prefi lter or systemic) or regional citrate anticoagulation is typically used. In selected

patients at risk of bleeding, either no anticoagulation or citrate should be used. Once renal replacement therapy is started, uncertainty exists about when to stop. No randomised controlled trials have addressed this issue. Findings from observational studies have suggested that urine output during treatment can be used to predict successful cessation of continuous renal replacement therapy. A spontaneous urine output of more than 500 mL per day seems to have suffi cient discrimination to be used in a trial of therapy cessation. Research is increasing into acute-kidney-injury-related extracorporeal blood purifi cation by means of adsorptive systems and the use of tubular cells containing bioreactors. Although early clinical studies off er some promise, much more work is needed before such treatments are widely applied. ***(Uchino S, et al., 2009)***

Prognosis

Mortality from acute kidney injury remains high, particularly in critically ill patients, in whom mortality was 53% in the ATN trial and 44.7% in the RENAL trial. Several large epidemiological studies have linked acute kidney injury with the later development of chronic kidney disease, end-stage kidney disease, and mortality. These results suggest that even a short episode of acute illness might contribute to long-term morbidity and mortality. Thus, the cost to the patient and to society of acute kidney injury might be greater than was previously thought. Whether this increased risk of chronic kidney disease shows the effect of acute kidney injury itself, or whether acute disease is a marker that identifies vulnerable patients, is unclear and requires further investigation as a public health priority. ***(Bellomo R, et al., 2003)***

Chronic Kidney Disease

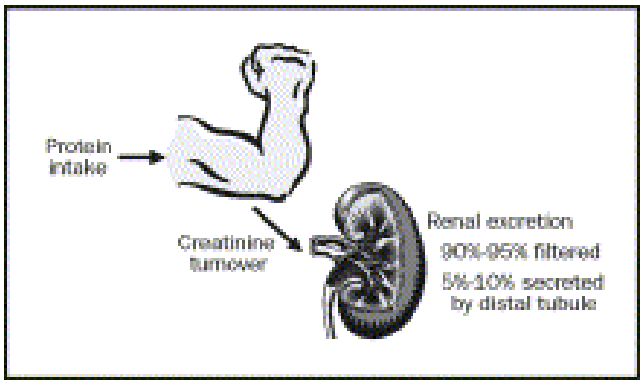
Chronic kidney disease (CKD), as defined by a reduction in the estimated glomerular filtration rate (GFR), is increasing in the United States, in part because of the greater prevalence of obesity and hypertension but in greater part because of improved longevity. Because GFR declines 1% per year for every year of life after the third decade, living longer means that it is possible to outlive one's renal function and to require renal replacement therapy to stay alive. Longevity increases the risk of developing diseases, such as diabetes, hypertension, and atherosclerotic vascular disease, that have direct adverse effects on kidney function***. (Kohli, HS, Bhat, A, Aravindan et al. 2006)***

Long life also increases the risk of exposure to nephrotoxic medications for other health conditions, such as arthritis (nonsteroidal anti-inflammatory drugs [NSAIDs]), infections (antibiotics), cancer (chemotherapy), gastroesophageal reflux disease (proton pump inhibitors), and coronary artery disease (radiocontrast agents***). (Liss, P, et al., 2006)***

MARKERS OF RENAL FUNCTION

The most commonly used measure of renal function (GFR) in clinical medicine is the serum creatinine level. To use the serum creatinine level as a marker of renal function, creatinine production and protein intake must be assumed to be constant (Figure). Creatinine excretion is due not only to filtration (90%-95%) by the kidney but also to secretion (5%-10%) by the distal tubule. As GFR decreases, the percentage of creatinine excretion due to secretion increases. In this circumstance, substances that block distal tubule secretion of creatinine (eg, trimethoprim, cimetidine, cefoxitin, flucytosine) may cause the serum creatinine level to increase abruptly, when in fact GFR has not changed at all. ***(Andreev, E, et al., 1999)***

Because they can confuse the assessment of kidney function, these agents are often avoided in the patient with CKD. Glomerular filtration rate can be estimated by measuring creatinine clearance using serum creatinine levels and a timed urine specimen. However, measuring creatinine clearance is time-consuming and fraught with errors of timing and collection, so other methods of estimating GFR, both those that rely on determining serum creatinine levels and those that do not, have been sought to replace the measured creatinine clearance.



FIGURE

Balance between muscle production and renal excretion of serum creatinine. As the glomerular filtration rate decreases, the percentage of creatinine excreted via secretion increases.

Multiple formulas exist to estimate renal function accurately by correcting for such factors as differences in muscle mass in men vs women or in African American vs white people and changes in muscle mass due to aging. The most commonly used are the Cockroft-Gault equation and the 4-variable and 6-variable Modification of Diet in Renal Disease (MDRD) equations. ***(Levey, AS, et al., 1999)***

Rule et al have argued that, because these formulas are derived from patients with renal disease, they may not predict renal function as well in patients without renal disease. Most clinicians use the MDRD equation because of its availability on the Internet, where one can simply plug in values for age, weight, race, and sex to receive an estimated GFR. It should be recognized that all these formulas have wide confidence intervals such that small changes in true GFR are hard to detect by this method. ***(Rule, AD, et al., 2006)***

An alternative serum marker, cystatin C, has been proposed as a marker of GFR. Cystatin C, an endogenous cysteine protease inhibitor, is freely filtered by the kidney and unaffected by renal tubules. However, serum levels are more variable than for creatinine, and the fact that serum levels can be affected by acute disease (malignancy, infection with human immunodeficiency virus) has left cystatin C without a defined role in clinical medicine. Estimates of GFR can be obtained from radioisotope and short clearance studies using infused substances, such as inulin or iothalamate. ***(Rule, AD, et al., 2006)***

These tests, which are too complex for regular clinical use, are not required because the estimated GFR serves the clinician well in most circumstances. Their primary clinical function is to help define whether a patient is at end-stage renal disease. All these estimates of renal function are harder to interpret during acute renal failure, which is characterized by an unstable association between creatinine production and renal excretion (changing renal function). ***(Traynor, et al., 2006)***

Where does the primary care physician find the previous measurements of serum creatinine levels that are needed to interpret the current value correctly? Sources of baseline serum creatinine values include laboratory work performed during previous physician visits, minor surgeries (appendix, tonsillectomy), physical examinations at the work-place or for purposes of insurance, and school or sports physical examinations, during which routine urinalysis is often performed to help ascertain the onset of kidney disease (proteinuria or microhematuria). Once it has been determined that the elevated serum creatinine level represents CKD, an effective approach is needed for identifying why such an increase occurred.

Evaluation of the patient

History

In taking the history of a patient with CKD, the clinician should attempt to determine when the onset of proteinuria and hypertension occurred and whether previous serum creatinine tests have been performed. Patients should also be questioned regarding voiding symptoms, such as hesitancy, decreased stream strength, or intermittent large and small voiding amounts, because these symptoms suggest obstructive uropathy. Every patient with an elevated serum creatinine level should be asked if they have a history of diabetes, arthritis, or medication exposure. Almost all NSAIDs, including over-the-counter forms and almost all antibiotics, have been reported to cause renal failure in at least 1 case report. ***(Perazella, et al., 2003)***

In fact, no NSAID can be declared "safe" with regard to renal failure. Previous use of chemotherapeutic agents, such as gemcitabine and cisplatin, or history of gastroesophageal reflux disease and proton pump inhibitor use should be identified. Recent radiographic studies using radiocontrast agents should also be considered when attempting to identify possible causes of an elevated serum creatinine level. ***(Liss, P, et al., 2006)***

Diagnostic Examination

The diagnostic examination for the patient with renal failure includes a few unique items. First, to test for prerenal azotemia, lying and standing blood pressure and pulse should be recorded. Funduscopic examination for findings of hypertension (Keith-Wagener-Barker) and diabetic changes should be performed. The ability to view the nondilated fundus is greatly

enhanced with the use of a specially designed ophthalmoscope. ***(Wagener, et al., 1939)***javascript:void(0);

During an examination specific to a diagnosis of increasing serum creatinine levels, the clinician should also check for evidence of volume overload (rales, third heart sound, lower-extremity edema), joint effusions or erythema, and splinter hemorrhages, as well as palpate for distended bladder above the symphysis pubis.

Laboratory Testing

Standard. Consider testing for creatinine phosphokinase and aldolase levels to determine that the elevated serum creatinine level retains its validity as a marker of renal function and does not reflect increased creatinine production (eg, rhabdomyolysis).

The standard work-up also includes a physician-performed urinalysis; measurement of levels of serum creatinine (usually with a full electrolyte panel), creatinine, and serum cholesterol (nephrotic syndrome); and a 24-hour urinary protein excretion test.

Subspecialty Evaluation. To determine whether systemic illness is the cause of renal disease, an antineutrophil cytoplasmic antibody panel, serum and urine protein electrophoresis, and fat aspiration for amyloidosis may be performed, as should serologic tests to determine C3 and C4 complement levels and to check for the presence of anti-nuclear antibody, rheumatoid factor, antiglomerular basement membrane antibody, and cryoglobulins. Although commonly performed, these tests only rarely reveal a systemic disease thought to be present without the serologic evidence, and even positive serologic findings do not obviate the need for renal biopsy. ***(Howard, AD, et al., 1990)***

However, positive serologic findings may make physicians more comfortable in recommending a renal biopsy. Although most renal biopsies are without incident, 50% of the patient's GFR could be lost if refractory bleeding requires nephrectomy.

Radiography

Renal ultrasonography with arterial Doppler studies is the single most important test for evaluating all patients with an elevated creatinine level. First and most importantly, it is the least invasive method for identifying obstructive uropathy, the most reversible form of renal failure. Second, it provides information on renal size. If the kidneys are smaller than 7 to 8 cm, then the likelihood of a reversible form of renal failure is extremely low. Large kidneys (>12-13 cm) have a specific differential diagnosis, including reversible conditions such as acute glomerulonephritis, infiltrative diseases of the kidney (leukemia, lymphoma, Hodgkin disease, multiple myeloma, and amyloidosis), andconditions without reversibility such as diabetic nephropathy, polycystic kidney disease, and obstruction. The Doppler component helps identify patients with bilateral renal artery stenosis, whose renal function would benefit from successful angioplasty.

Management of chronic kidney disease

Treatment of chronic kidney disease (CKD) aims to slow progression to endstage renal disease (ESRD) and to prepare for ESRD. Because the symptoms of chronically progressive renal failure develop slowly, therapy of CKD is usually directed at an asymptomatic condition detected only by laboratory testing. The task is also made more difficult as it usually represents a late attempt at prevention. That is, the major causes of ESRD, hypertension, and type 2 diabetes can themselves be avoided to some degree by primary preventive measures such as diet, weight control,

and exercise. Furthermore, once hypertension or diabetes is manifest, their renal complications can be mitigated by secondary prevention efforts aimed at blood pressure and glycemic control.

Thus, treatment of CKD often represents an example of tertiary prevention in populations who have failed the first lines of prevention but who are still relatively asymptomatic. These features make CKD therapy a formidable task in practice. However, over the past 20 years, some effective treatments of CKD have developed. These can delay and, in some cases, prevent ESRD ***(Turner et al., 2012).***

The notion of CKD as a single entity with generic therapy is a simplification but a useful one. Admittedly, some forms of CKD, especially inflammatory and autoimmune ones, require special treatments. However, even these approaches are usually applied in addition to those used for the most common hypertensive and diabetic causes. Viewing CKD as a single process rests both on the effectiveness of therapy across a range of primary diseases and on the data, suggesting that final common physiological pathways underlie the progression of CKD irrespective of initiating insult ***(Hostetter, 2003, Zandi-Nejad and Brenner, 2005, and Remuzzi et al., 2006).***

Cardiovascular disease (CVD) is now well known to be common and often fatal in people with CKD ***(Go et al., 2004a, van, V et al., 2011).***

Hence, careful attention to reducing traditional CVD risk factors in CKD is of great importance. Nevertheless, delay of ESRD remains a primary goal of CKD therapy simply because specific treatments to avoid CVD in this population do not currently exist. Standard methods of CVD prevention should be assiduously applied in CKD. Similarly, people with CKD should receive health maintenance applicable to the general population such as cancer screening and vaccinations ***(Turner et al., 2012).***

The definition of CKD has itself received considerable attention. The most important consequence of the definition is its implications for therapy of an individual patient. Current treatment options are broadly initiated across CKD populations because they are relatively inexpensive and safe. Given the low potential risk for individuals treated with these medications, and the absence of sophisticated prognostic tools, extended debate of CKD definitions is largely unimportant for clinical practice. If more toxic or expensive therapies are forthcoming, or when better markers of progression develop, then the definition may need refinement. At present, we regard the simple definition of CKD as an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m2 and/or persistent albuminuria >30 mg of urinary albumin per gram of urinary creatinine as adequate ***(Ramirez-Rubio et al., 2013).***

I. MANAGEMENT OF ETIOLOGY

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

Angiotensin-converting enzyme (ACE) inhibitors were the first treatment shown to be effective in slowing the progression of diabetic nephropathy by Lewis et al. The work followed on animal studies by several laboratories, most notably that of Barry Brenner in the 1980s ***(Zatz et al., 1987).***

ACE inhibitors and angiotensin II receptor blockers (ARBs) are standard drugs for primary hypertension. However, they are each especially effective in slowing the progressive decay of GFR in CKD ***(Lewis et al., 1993, Brenner et al., 2001, Jafar et al., 2001 and, Lewis et al., 2001a).***

Diabetic nephropathy has been the disease state most studied with these agents. In both diabetes mellitus type 1 and type 2, slowing the rate

of progressive renal injury with renin–angiotensin–aldosterone system (RAAS) inhibition has been intimately associated with the stabilization or reduction of proteinuria ***(Lewis et al., 1993, and Brenner et al., 2001).***

These findings have been demonstrated in patients with microalbuminura and macroalbuminuria ***(Lewis et al., 1993, and Ravid et al., 1996).***

In nondiabetic renal diseases, the data for the benefits of RAAS inhibition on progression of CKD are strongest in those patients with proteinuria >1000 mg/day according to a meta-analysis ***(Jafar et al., 2003).***

The AASK trial further supports this in African Americans with hypertensive nephropathy ***(Appel et al., 2010).***

The benefit of RAAS inhibition in subjects with nondiabetic kidney disease without proteinuria is less clear. In certain disease states such as autosomal dominant polycystic kidney disease, there may be little to no benefit from ACE inhibitors and ARBs despite measurable reductions in proteinuria ***(Jafar et al., 2005b).***

This is a current topic of investigation in the HALT PKD trial *(Chapman, 2008)*. The exact nature of the relationship between proteinuria and progressive renal injury remains a topic of debate ***(Glassock, 2010).***

It may be misleading to interpret reductions in albuminuria as a surrogate for improved renal function. Although some authors argue that experimental evidence suggests that proteinuria has direct toxic effects, currently there is no consensus that the available evidence clearly establishes a cause and effect role ***(Zoja et al., 2003, and Abbate et al., 2006).***

For this reason, the significance of the antiproteinuric properties of ACE inhibitors and ARBs is unclear ***(Turner et al., 2012).***

On the contrary, there are two widely accepted mechanisms by which ACE inhibitors and ARBs are understood to be beneficial agents in CKD: hemodynamic/antihypertensive actions and anti-inflammatory/antifibrotic actions. Their reduction of angiotensin II (AngII) levels (and subsequent reduction in aldosterone levels) is central to both of these pathways. In many animal models of CKD, glomerular capillary pressures are elevated. ACE inhibitors and ARBs reduce this capillary hypertension by both reducing arterial perfusion pressure and relaxation of the efferent arteriole, the dominant site of AngII action. Relief from this excessive capillary pressure likely prevents mesangial cell proliferation and matrix production, as well as podocyte loss ***(Hostetter, 2003).***

Subsequent to the description of beneficial hemodynamic effects, investigators began to describe the RAAS as a proinflammatory and profibrotic mediator. AngII activates NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells), upregulates adhesion molecules, and may directly stimulate proliferation of lymphocytes ***(Ruster and Wolf, 2006, and Sowers et al., 2009).***

The net result of these actions is a local inflammatory environment in areas where AngII is in high concentration, namely the kidney. AngII may also foster fibrosis via interactions with transforming growth factor-β (TGF-β) and the induction of extracellular matrix proteins such as type I procollagen, fibronectin, and collagen type IV ***(Turner et al., 2012).***

In addition, animal models have implicated aldosterone to be directly involved with mechanisms of endothelial dysfunction, inflammation, and fibrosis ***(Nishiyama and Abe, 2006).***

Table 1 gives a more complete list of the proposed inflammatory mechanisms mediated by the RAAS. Using ACE inhibitors and ARBs to

quell these hostile attacks in the kidney is likely an important factor in slowing the progression of CKD.

Table 1 Reported nonhemodynamic effects of renin –angiotensin aldosterone system

Mechanism	Comment	Mediator
Stimulation of NF-κB	A transcription factor resulting in a cascade of cytokines and other proinflammatory factors	AngII, AngIII, AngIV
Stimulation of ETs-1	A mediator of vascular inflammation with Tcell and macrophage/monocyte recruitment	AngII
Adhesion molecules Vascular cellular adhesion molecule 1 Intracellular adhesion molecule 1 Integrins	Facilitates adhesion of inflammatory cells to capillary walls	AngII
Cell proliferation Mesangial cells Glomerular endothelial cells Fibroblasts	Enhances structural renal damage and fibrosis	AngII /Aldo
Apoptosis	As opposed to cellular proliferation, under certain circumstances, AngII instead induces apoptosis; how this is regulated is unclear	AngII
Increased TGF-β expression	An important protein that results in cascading effects central to inflammation and fibrosis	AngII /Renin
Increased connective tissue growth factor	Can occur by direct stimulation by AngII or via TGF-β upregulation	AngII
Increased ECM products Type I procollagen Fibronectin Collagen type IV	Result in ECM accumulation and are pivotal factors that contribute to fibrosis	AngII

Mechanism	Comment	Mediator
Increased metalloproteinase inhibitors Plasminogen activator inhibitor-1 Tissue inhibitor of matrix metalloproteinases	Also results in ECM accumulation due to decreased turnover	AngII
Ac-SDKP hydrolysis	Increases fibrosis and inflammatory Cell infiltration	ACE
Reactive oxygen species	***Leads to cellular damage***	***Aldo***
MAPK activation	Contributes to mesangial injury and renal fibrosis	AngII/Aldo

Abbreviations: ACE, angiotensin-converting enzyme; Ac-SDKP, N-acetyl-serylaspartyl- lysyl-proline; Aldo, aldosterone; Ang, angiotensin; ECM, extracellular matrix; ETs-1, endothelins-1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κ- light-chain-enhancer of activated B cells; TGF-β, transforming growth factor-β.

As ACE inhibitors and ARBs each slow progression individually, the question has arisen as to whether the combination would provide additional advantage. This issue has not been definitively settled. One early report of the COOPERATE trial claimed that the combination was superior to the individual drugs ***(Nakao et al., 2003).***

However, these results and their analyses have been brought into question and retracted ***(Bidani, 2006, and Kunz et al., 2008).***

These events make any conclusions drawn from the COOPERATE trial invalid. An analysis of a study designed to examine cardiovascular end points in subjects with cardiovascular disease but generally good renal function (the ON TARGET study) found lesser proteinuria with

combination ACE inhibitor and ARB therapy, but no benefit in terms of preventing a decline in GFR ***(Mann et al., 2008).***

This study raises a couple of interesting findings. First, the relationship between improved proteinuria and worsening GFR contributes further reason to question the significance of reduced albumin excretion as a meaningful clinical outcome. Second, the lack of improved renal end points in those receiving dual therapy questions the validity of this treatment strategy for slowing CKD progression. A high burden of renal vascular atherosclerosis in the participating subjects may have contributed to these results, and it remains unclear whether these findings can be directly applied to broader populations with renal dysfunction. Currently, several trials are underway to address this, but at present there are no firm data to support the use of combination therapy ***(Chapman, 2008, and Fried et al., 2009).***

Aldosterone contributes along with AngII to the adverse actions of the RAAS in progressive CKD. Recognition of the deleterious effects of aldosterone has led to attempts to selectively block it by using the mineralocorticoid receptor blockers ***(Ponda and Hostetter, 2006).***

A large number of studies in experimental animals have supported this approach. Several trials in human subjects with CKD have shown a reduction in proteinuria when aldosterone blockade was added to an ACE inhibitor or ARB ***(Ponda and Hostetter, 2006, Bomback et al., 2008, Mehdi et al., 2009, and Navaneethan et al., 2009).***

However, there is not yet a large enough trial to assess the effects on decline in GFR. Moreover, hyperkalemia is more frequent. Thus, there are no sufficient data to recommend the addition of aldosterone blockade to standard therapy in CKD ***(Ramirez-Rubio et al., 2013).***

Inhibition of renin is yet another means of interrupting the RAAS. Addition of a renin inhibitor to an ARB reduced proteinuria in diabetic nephropathy ***(Parving et al., 2008).***

The diminution of proteinuria was with little if any further reduction in blood pressure and no additional side effects were noted with the combination. A larger and longer trial is underway to test the value of rennin inhibitor addition to ACE inhibitors or ARBs using cardiovascular and renal end points ***(Parving et al., 2009).***

In summary, blockade of the RAAS with ACE inhibitors or ARBs has proven effective in retarding progression of CKD. Studies are ongoing to assess the value of interrupting the pathway simultaneously at multiple sites, but such approaches have, at this time, not been proven more effective than the use of ACE inhibitors or ARBs and have not been adequately assessed for safety ***(Turner et al., 2012).***

Blood pressure

Although there is a considerable amount of overlap when considering the beneficial effects of RAAS inhibition and blood pressure control, it is important to appreciate them as two separate treatment targets. The reductions in arterial and glomerular capillary pressure affected by antihypertensive medications dictate their beneficial effects. However, the optimal target arterial pressure in CKD is largely a matter of opinion. Current guidelines suggest a target of <130/80 mm Hg for patients with CKD, a more stringent control than the 140/90 mm Hg recommended for the general population. A meta-analysis was performed to specifically address this question ***(Upadhyay et al., 2011).***

The study included results from 2272 subjects with nondiabetic renal disease involved in the MDRD, AASK, and REIN-2 trials. Overall, no benefits in renal outcomes, cardiovascular outcomes, or death were

obtained in patients with CKD who were treated to a goal blood pressure of 125–130/75–80 mm Hg as compared with 140/90 mm Hg. From subgroup analysis, proteinuria did appear to be an effect modifier. Participants with daily proteinuria >300 mg in the AASK trial and >1000 mg in the MDRD trial did show a benefit. The ACCORD trial in type 2 diabetes compared a goal systolic blood pressure of 140 mm Hg with one of 120 mm Hg and found no overall benefit to the lower goal ***(Cushman et al., 2010).***

Albuminuria was less with the lower pressure but eGFR was also lower at the end of the study in this group. However, the trial did not target people with CKD, and on average the starting eGFRs were >90 ml/min per 1.73 m2 and albumin excretion less than the microalbumuria level. Whether a goal of 120 mm Hg systolic pressure is desirable in the CKD population is unknown but is a question to be addressed by the SPRINT trial, which will recruit a large fraction of subjects with CKD. Until we have these results, the present guideline of 130/80 mm Hg seems reasonable, especially for those patients with higher amounts of proteinuria ***(Turner et al., 2012).***

If first-line therapy with an ACE inhibitor or ARB fails to achieve the target of 130/80, and often it will not, the choice of the second agent is also largely a matter of opinion. Addition of a diuretic has physiological appeal. In short-term studies, the addition of a thiazide diuretic to an ARB showed additional reduction of proteinuria in CKD, possibly suggesting further renal protection. Often it is said that thiazide diuretics lose potency in later stages of CKD compared with loop diuretics. There is little evidence for this contention ***(Dussol et al., 2005).***

Many people with CKD will require more than the combination of a diuretic and ACE inhibitor or ARB to reach target blood pressures. Further choices are similarly not based on long-term studies of progression, but β-

blockers, calcium channel blockers, and/or central sympatholytic agents are satisfactory. Targeting blood pressure <130/80 mm Hg is recommended, but will often require two or more drugs ***(Ramirez-Rubio et al., 2013).***

GLYCEMIC CONTROL IN DIABETES

Glycemic control reduces the progression of renal disease as judged by the mitigation of increasing albuminuria in both type 1 and type 2 diabetes ***(Bilous, 2008, and Patel et al., 2008).***

For example, in the DCCT, in type 1 diabetes, strict glycemic control compared with usual control lessened the progression from microalbuminuria (30– 299 mg albumin per g creatinine) to macroalbuminuria (>300 mg albumin per g creatinine). Similarly, in the ACCORD trial, transitions to microalbuminuria and macroalbuminuria were diminished by stringent glycemic control. However, the incidence of ESRD was not different between levels of glycemic control in ACCORD or ADVANCE, another study of glycemic control in type 2 diabetes, and the incidence of ESRD has been low in follow-ups to DCCT ***(Patel et al., 2008).***

No large-scale studies have specifically tested the benefits of glycemic control in diabetic CKD with GFR of <60 ml/min per 1.73 m2 or macroalbuminuria. Thus, although attention to glucose control seems to afford renal protection, this has been gauged largely by changes in albuminuria. Evidence that glucose control can forestall ESRD in people with established diabetic CKD is lacking. The exact best level of glycemic control is uncertain. Because of overall mortality risks with very stringent glycemic control, current guidelines call for hemoglobin A1c levels of <7.0%. At present, maintaining hemoglobin A1c of <7.0% remains reasonable for people with established diabetic CKD ***(Ruggenenti et al., 2012).***

II. METABOLIC DERANGEMENTS OF CKD

Acid base

Although the acidosis of CKD results from decreased renal ammoniagenesis, ammonia production per residual GFR in patients and per residual nephron in animals actually rises as CKD progresses ***(Simpson, 1971, Schoolwerth et al., 1975, and Simon et al., 1985).***

Data in rat models of renal disease have suggested that excess ammoniagenesis per residual nephron causes tubulointerstitial injury because of the interaction of ammonia with complement component, C3 ***(Nath et al., 1985, and Tolins et al., 1987).***

Bicarbonate supplementation reduced injury in some but not all rat models tested ***(Throssell et al., 1995, Throssell et al., 1996, and Torres et al., 2001).***

An analysis of the relation of serum bicarbonate to progression of renal disease in a data set including over 5000 outpatients found that low serum bicarbonate level was strongly associated with subsequent progression of kidney disease ***(Shah et al., 2009).***

Obviously, this strong association does not prove a causal relationship, and a clinical trial is needed to determine whether amelioration of acidosis would lessen progression. ***(Kovesdy et al., 2009)*** have reported that lower serum bicarbonate was associated with mortality in a cohort with CKD.

Several relatively small trials of the effects of bicarbonate supplementation on renal disease progression have been reported. The first trial was randomized, but not blinded or placebo controlled, and studied people with advanced CKD ***(de Brito-Ashurst et al., 2009).***

It comprised 129 subjects with estimated creatinine clearance (CrCl) of <30 ml/min who were randomized to receive either sodium bicarbonate or continuation of usual care. The treated group received an average of 14 mEq/day of bicarbonate. The most striking result was a 6.5% vs. 33% incidence in ESRD over a 2-year follow-up, treated vs. control, respectively. Another trial studied subjects with relatively high eGFR (~75 ml/min) and assigned 40 subjects each to sodium bicarbonate supplementation, sodium chloride supplementation, or nothing ***(Mahajan et al., 2010).***

Sodium bicarbonate at a dose of 0.5 mEq per kg body weight per day was associated with fewer subjects developing more advanced disease over 5 years (<60 ml/min). The rate of decline in eGFR was significantly less in those receiving sodium bicarbonate as compared with those receiving sodium chloride or placebo. Interestingly, urinary endothelin excretion declined with bicarbonate treatment. In an uncontrolled trial comparing 30 patients with eGFR <60 ml/min given sodium citrate for 24 months with 29 CKD patients not treated with alkali, eGFR was higher at the end of the study in the treated group ***(Phisitkul et al., 2010).***

An effect of alkali on progression of kidney disease in these patients may have been mediated by a reduction in endothelin secretion. More data suggest that treatment with alkali in CKD patients reduces both endothelin and aldosterone secretion ***(Wesson et al., 2011).***

Thus, the effects of alkali supplementation on the progression of renal disease have been tested only in small studies with less than optimal design but with encouraging results. Present guidelines suggest treating patients with alkali when serum bicarbonate level decreases to <22 mEq/l. Although this is opinion based, the available human data and the prior animal studies raise the possibility that such treatment could retard progression ***(Turner et al., 2012).***

Phosphate

Evidence suggests that fibroblast growth factor-23, a phosphaturic hormone, increases early in CKD to maintain phosphorous balance ***(Wolf, 2010).***

Regardless of this, without intervention, hyperphosphatemia regularly appears as CKD progresses. Control of hyperphosphatemia with dietary restriction and phosphate binders have long been mainstays of therapy directed at preventing bone disease. However, animal studies more than 30 years ago also suggested that hyperphosphatemia hastened progression to ESRD by causing calcium–phosphate crystal deposition within the renal interstitium ***(Alfrey, 2004).***

More observational studies have found that elevated phosphate associates with more rapid decline in eGFR, and also that separately it associates with CVD in CKD as well as the general population ***(Levin et al., 2008, Foley, 2009,Tonelli et al., 2009, and Bellasi et al., 2011).***

In parallel to this, additional studies have also linked elevated serum fibroblast growth factor-23 with a greater risk for progression of CKD ***(Fliser et al., 2007, and Titan et al., 2011).***

In years, the proposed pathogenetic mechanisms for extraosseous toxicity have grown to suggest a role for hyperphosphatemia in vascular and cardiac calcifications, both of which are common in advanced CKD. These calcifications may be mediated through hormonal reactions to phosphate such as the phosphatonins and cellular transformations of vascular smooth muscle cells to those with more bone phenotypes ***(Hruska et al., 2009).***

In any case, interventional trials to test the efficacy of phosphate-lowering strategies for either slowing CKD progression or preventing CVD are lacking. Thus, phosphate control when used in CKD must be based on data for ameliorating bone outcomes, which are themselves modest, or at best opinion based on animal and epidemiologic work. Further trials are needed ***(Turner et al., 2012).***

Vitamin D

Deficiency of 1,25-dihydroxyvitamin D may be expected with advancing CKD, as the kidney is the site of its synthesis. However, low levels of its precursor 25-hydroxyvitamin D have been linked epidemiologically to more rapid progression of CKD ***(Melamed et al., 2009).***

The physiological actions of vitamin D are multiple and extend well beyond its classic effects on calcium, phosphate, and bone ***(Gal-Moscovici and Sprague, 2010).***

For example, vitamin D suppresses renin secretion, and this action has been proposed as beneficial in CKD ***(Zhang et al., 2011a).***

There are no long-term trials of vitamin D supplementation in progressive renal disease using the strongest outcomes such as reduction of GFR or incidence of ESRD. However, in the VITAL study, a synthetic vitamin D analog, paricalcitol, did lower albuminuria in subjects with diabetic nephropathy ***(de et al., 2010).***

In this study, reduced albuminuria was associated with a decrease in blood pressure and an increase in eGFR, suggesting that vitamin D–mediated rennin suppression may have been the major contributing mechanism. Clearly, clinical trials are needed to test the effect of vitamin D on hard outcomes, and especially to test inexpensive forms such as nutritional vitamin D, cholecalciferol ***(Turner et al., 2012).***

Parathyroid hormone

Secondary hyperparathyroidism also regularly attends progressive CKD and is at least partly a consequence of hyperphosphatemia and vitamin D deficiency. Elevated PTH levels have also been suggested as toxic even beyond their capacity to induce bone loss ***(Rodriguez and Lorenzo, 2009).***

However, an analysis of published literature found that the evidence for links between parathyroid hormone (PTH) and CVD or mortality was poor. The usual recommendations for phosphate and vitamin D should mitigate secondary hyperparathyroidism, but whether this slows progression of CKD or lessens CVD is uncertain. In principle, targeted suppression of PTH with a calcimimetic would be an attractive means of testing the role of PTH in extraosseoussequelae of CKD. However, to date, the role of PTH in such events is untested ***(Palmer et al., 2011).***

Uric acid

Epidemiological studies have often found an association between hyperuricemia and CVD ***(Feig et al., 2008a, Tangri and Weiner, 2010, and Wen et al., 2010).***

The basis for this association is uncertain. However, over the past several years, hypertension has been ascribed to hyperuricemia based largely on animal studies, but human studies are few ***(Feig et al., 2008a).***

One study of newly diagnosed hypertensive adolescents found that lowering uric acid with allopurinol reduced blood pressure ***(Feig et al., 2008b).***

With regard to CKD, hyperuricemia predictably appears as GFR declines. Furthermore, uric acid is clearly toxic to the kidney in very high concentrations as in tumor lysis. Whether more modest elevations of uric acid are detrimental is more controversial. Observational studies have found modest associations of hyperuricemia with decline in renal function ***(Obermayr et al., 2008).***

One small randomized but unblinded trial involved 25 patients with mixed causes of CKD. Subjects were assigned to receive either allopurinol or conventional treatment ***(Siu et al., 2006).***

The investigators succeeded in lowering uric acid, but in this study blood pressure was not affected. The serum creatinine tended to remain lower in the allopurinol-treated group, but was not statistically different from that in the control group. A combined end point of incident ESRD and 40% rise in creatinine was significantly greater in the untreated group. A second randomized control study involving 113 patients, again with mixed causes of CKD, also showed a favorable effect induced by allopurinol ***(Goicoechea et al., 2010).***

In this study, those receiving allopurinol had a mean eGFR increase of 1.3 ml/min per 1.73 m2 over a period of 24 months. This was a statistically significant difference when compared with the mean eGFR decrease of 3.3 ml/min per 1.73 m2 observed in the control group. These findings occurred independent of any differences in blood pressure between the two groups. These studies, although suggestive, are not sufficiently robust to recommend allopurinol as a means of slowing progression. Larger studies might be warranted except that allopurinol has a rather high risk for allergic reactions that can be severe. If better alternatives for uric acid–lowering drugs were available, then larger trials would be attractive ***(Turner et al., 2012).***

Anemia

Several studies have tested the efficacy and safety of therapy of anemia with erythropoietin congeners in CKD before dialysis ***(Parfrey, 2011).***

The largest and most persuasive study TREAT randomized 4038 subjects with CKD due to type 2 diabetes to a target hemoglobin of 13 g/dl, or placebo with darbepoieten rescue if the level dropped below 9 g/dl ***(Pfeffer et al., 2009).***

The baseline eGFR was ~35 ml/min per 1.73 m2 for each of the two groups. Except for more strokes in the higher hemoglobin group, there were no differences in cardiovascular or renal outcomes between the two groups. Approximately 16% of the subjects in each group developed ESRD over the 4 years of study. Thus, maintaining hemoglobin levels at 13 g/dl is unwarranted. The lower hemoglobin group had an average level of 10.6 g/dl but received more transfusions. The optimal level is not clear. Current guidelines call for levels between 10 and 12 g/dl in ESRD, and this also seems reasonable for patients with CKD predialysis. However, lower levels might be equally good, but in practice a small percentage of CKD patients require treatment for severe anemia before ESRD ***(Turner et al., 2012).***

Dietary protein

Dietary protein restriction was one of the earliest therapeutic maneuvers used in CKD. In addition to contributing to alterations in phosphorous, metabolic acidosis, and uric acid as described previously, other proposed mechanisms for renal injury from increased dietary intake include altered hemodynamics, leading to glomerular hyperfiltration, and reduced cytokine-mediated fibrosis ***(Woods, 1993, and Nakamura et al., 1994).***

Protein restriction does seem to ameliorate some of the symptoms of advanced CKD, and many animal studies showed that it reduced renal injury ***(Curhan and Mitch, 2008).***

However, clinical trials have been less clear as to its efficacy in slowing progression. A large analysis of the available clinical trial literature concluded that low-protein diets reduced the incidence of ESRD in nondiabetic patients ***(Fouque and Laville, 2009).***

Because of varying study designs, this review could not define an optimal level of intake. Properly constructed and monitored protein restriction can be safe ***(Curhan and Mitch, 2008).***

Probably because successful and safe protein restriction requires much effort or physicians, dieticians, and patients, it is not sedulously practiced. Provided that malnutrition is avoided and the burden is acceptable to the individual patient, a target of 0.8 g of protein per kg body weight per day seems reasonable. However, careful monitoring of nutritional status and attentive dietary care is needed if protein restriction is attempted ***(Turner et al., 2012).***

LIPID-LOWERING THERAPY

Abnormal lipid metabolism often accompanies renal dysfunction. Although hyperlipidemia does not in itself seem to cause primary renal disease, it may contribute to the progression of CKD. The hypothesis of lipid nephrotoxicity was first generated by ***Moorhead et al., 1982).***

The proposed mechanisms parallel the injury events that lead to atherosclerosis in other vascular beds. In the presence of lipids, mesangial cells are stimulated to recruit macrophages through the production of chemokines ***(Rovin and Tan, 1993).***

Activated mesangial cells and accumulated macrophages subsequently release oxygen radical species that lead to oxidized low-density lipoproteins. These oxidized low-density lipoproteins have been shown to stimulate proinflammatory and profibrotic cytokines ***(Keane, 2000).***

A likely integral component to this process is the phagocytosis of lipoproteins by macrophages and mesangial cells to produce foam cells. As evidence for this, foam cells are frequently found in sclerotic regions of glomeruli, as well as areas of interstitial fibrosis ***(Magil, 1999).***

In addition, mesangial cell proliferation may also be directly stimulated by low-density lipoproteins and triglyceride-rich lipoproteins ***(Nishida et al., 1999).***

Experimental studies in animals and observational data in humans support the hypothesis that lipids contribute directly to renal injury and progression of CKD. Rats fed high-cholesterol diets were found to have greater amounts of glomerulosclerosis and tubulointerstitial damage compared with those fed standard diets ***(Kasiske et al., 1990, and Guijarro et al., 1995).***

In humans, a number of epidemiological studies have suggested that elevated cholesterol and triglyceride levels are associated with a more rapid progression of renal dysfunction ***(Ravid et al., 1998, Appel et al., 2003, and Schaeffner et al., 2003).***

Given this, lipid-lowering therapy to slow the progression of CKD has generated a great deal of interest in the nephrology community. Although a number of different classes of these medications have been studied, the pertinent data revolve around HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors (statins). This class of medication seems to offer a potential benefit not just by way of decreasing the lipoprotein burden within tissues, but also by way of their additional anti-inflammatory affects. In animal studies, statin therapy has been shown to reduce macrophage recruitment into the glomerulus, limit expression of inflammatory factors including chemokines, cytokines, and adhesion molecules, and decrease fibrosis and mesangial cell expansion ***(Fried, 2008).***

These beneficial effects have been seen across a number of disease models including diabetic nephropathy, focal glomerulosclerosis, cyclosporine nephrotoxicity, and chronic allograft dysfunction ***(Kasiske et al., 1988, Ota et al., 2003, Li et al., 2005, and Zhang et al., 2007).***

Data in human trials supporting the benefits of statin therapy for slowing the progression of CKD have been less convincing. In a meta-analysis of 39,704 patients from 27 randomized, controlled, and crossover studies, treatment with statins resulted in a small but statistically significant favorable effect on yearly decline in eGFR (1.22 ml/min/year slower in statin recipients as compared with placebo) ***(Sandhu et al., 2006).***

In a subgroup analysis, those patients with cardiovascular disease were the most likely to benefit, whereas those with diabetes or hypertensive nephropathy or glomerulonephritis were not found to have a statistically significant benefit. The GREACE study evaluated the effects of a structured care algorithm for titrating atorvastatin to reach the low-density lipoprotein level of <100 mg/dl vs. usual care in the secondary prevention of major cardiac events.

A post hoc analysis evaluated the effects of statin therapy on change in renal function. For those patients who received atorvastatin as part of the structured care group the CrCl increased by 12%, and for those who received various statins as part of the usual care group the CrCl increased by 4.9%. In contrast, those who did not receive any statins had a decrease in CrCl of 5.2%. These results represent the largest benefit of any trial to date; however, it is important to keep in mind that the study design and the fact that this was a post hoc analysis invites certain bias. Another meta-analysis of 15 studies including 1384 subjects found that those treated with statins were more likely to have reductions in albuminuria or proteinuria; however, no hard clinical outcomes were reported ***(Douglas et al., 2006).***

The completed Study of Heart and Renal Protection (SHARP) is the largest randomized controlled trial to date to study the effects of statin therapy on progression of CKD ***(Baigent et al., 2011).***

The study involved over 9438 participants, 6382 of whom had CKD and were not on hemodialysis. Comparing those who received simvastain

20 mg plus ezetimibe 10 mg with those who received placebo, there was no difference in the risk of those with CKD to progress to ESRD. Although the study did suggest that lipid-lowering medications are beneficial in predialysis CKD patients to prevent major cardiovascular events, this is the strongest evidence to date to demonstrate a lack of benefit in slowing CKD progression with these agents. Thus, despite a reasonably conceived hypothesis, and supporting experimental evidence in animal studies, current human data do not convincingly show a significant benefit from statins for altering the disease course of CKD ***(Turner et al., 2012).***

CRS type 1 (acute CRS)

Type 1 CRS is characterized by a rapid worsening of cardiac function, leading to acute kidney injury (AKI). Acute heart failure (HF) may be divided into 4 subtypes: hypertensive pulmonary edema with preserved left ventricular (LV) systolic function acutely decompensated chronic HF, cardiogenic shock, and predominant right ventricular failure ***(A. Mebazaa, M. et al., 2008).***

Type 1 CRS is a common occurrence. More than 1 million patients in the U.S. are admitted to the hospital every year with either de novo acute HF or acutely decompensated chronic HF ***(G.A. Haldeman, et al., 1995)***.

Among these patients, pre-morbid chronic renal dysfunction is a common occurrence and predisposes them to AKI ***(K.F. Adams Jr, et al., 2005 and G.C. Fonarow, et al., 2007).*** (Fig. 1).

The clinical importance of each mechanism is likely to vary from patient to patient (e.g., acute cardiogenic shock vs. hypertensive pulmonary edema) and situation to situation (acute HF secondary to perforation of a mitral valve leaflet from endocarditis vs. worsening right HF secondary to noncompliance with diuretic therapy). In acute HF, AKI appears to be more severe in patients with impaired LV ejection fraction compared with those with preserved LV function, achieving an incidence >70% in patients with cardiogenic shock ***(P. Jose, et al., 2006).***

Impaired renal function is consistently found as an independent risk factor for 1-year mortality in acute HF patients, including patients with ST-segment elevation myocardial infarction ***(A. Goldberg, et al., 2005).***

A plausible reason for this independent effect might be that an acute decline in renal function does not simply act as a marker of illness severity but also carries an associated acceleration in cardiovascular pathobiology

through activation of inflammatory pathways ***(T. Berl, et al., 2006, and H. Tokuyama, et al., 2007).***

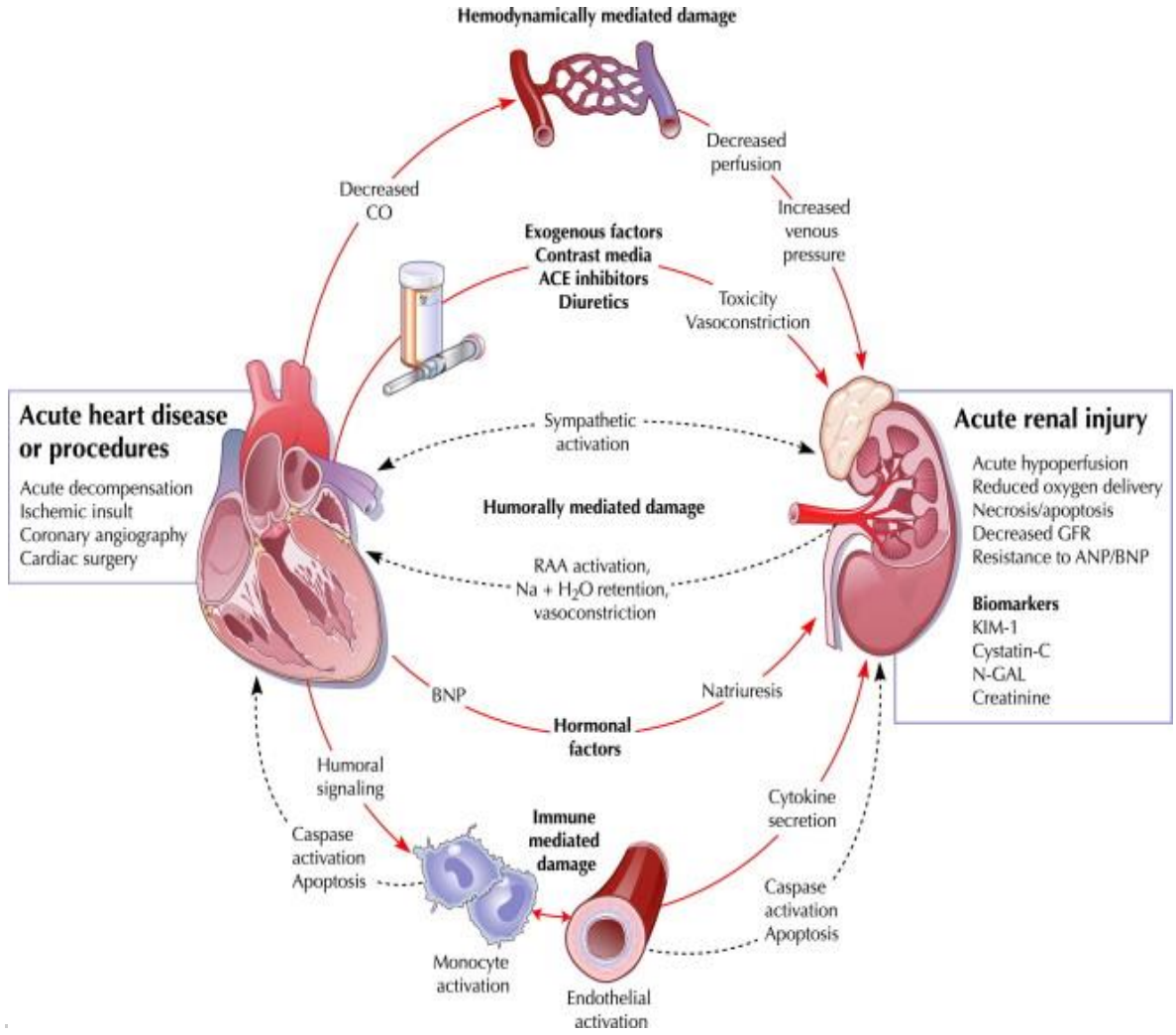


Figure 4. CRS type 1

CRS Type 1

Pathophysiological interactions between heart and kidney in type 1 cardiorenal syndrome (CRS) or "acute CRS" (abrupt worsening of cardiac function, e.g., acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury. ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CO = cardiac output; GFR = glomerular filtration rate; KIM = kidney injury molecule; N-GAL =

neutrophil gelatinase-associated lipocalin; RAA = renin angiotensin aldosterone. Figure illustration by Rob Flewell.

In CRS type 1, a salient clinical issue is how the onset of AKI impacts on prognosis and treatment of acute HF. The first clinical principle is that the onset of AKI in this setting implies inadequate renal perfusion until proven otherwise, which should prompt clinicians to consider the diagnosis of a low cardiac output state and/or marked increase in venous pressure leading to kidney congestion through the use of physical examination, ancillary signs, imaging, and laboratory findings.

The second important consequence of type 1 CRS is decreased diuretic responsiveness. In a congestive state, decreased response to diuretics may result from the physiological phenomena of diuretic braking (diminished diuretic effectiveness secondary to postdiuretic sodium retention) and post-diuretic sodium retention ***(D. H. Ellison. 1999)***.

In addition, concerns of aggravating AKI by the administration of diuretics at greater doses or in combination also can act as an additional, iatrogenic mechanism. Diuretics are best provided to HF patients with evidence of systemic fluid overload with the goal of achieving a gradual diuresis. Loop diuretics may be titrated according to renal function, systolic blood pressure, and history of chronic diuretic use. High doses may cause tinnitus, and a continuous low-dose diuretic infusion might be more efficient ***(P.A. Howard, et al., 2001)***.

Measurement of cardiac output (arterial pressure monitoring combined with pulse contour analysis or by Doppler ultrasound) and venous pressure may help ensure adequate and targeted diuretic therapy and allow safer navigation through the precarious situation of combined HF and AKI. ***(H.I. Opdam, et al 2007, L. Wan, et al., 2005 and H.B. Nguyen, et al., 2006)***

If diuretic-resistant fluid overload exists despite an optimized cardiac output, removal of isotonic fluid can be achieved by the use of

extracorporeal ultrafiltration ***(C. Ronco, et al., 2004 and Costanzo MR, et al., 2007).***

The presence of AKI with or without concomitant hyperkalemia may also affect patient outcome by inhibiting the prescription of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone inhibitors (drugs that have been shown in large randomized controlled trials to increase survival in the setting of heart failure and myocardial infarction) However, provided there is close monitoring of renal function and potassium levels, the potential benefits of these interventions often outweigh their risks, even in these patients. ***(A. Verma, et al., 2007)***.

The acute administration of beta-blockers in the setting of type 1 CRS generally is not advised. Such therapy should wait until the patient has stabilized physiologically and until concerns about a low output syndrome have been resolved. In some patients, stroke volume cannot be increased, and relative or absolute tachycardia sustains the adequacy of cardiac output. Blockade of such compensatory tachycardia and sympathetic system-dependent inotropic compensation can precipitate cardiogenic shock with associated high mortality ***(Z.M. Chen, et al., 2005)***.

Particular concern applies to beta-blockers excreted by the kidney, such as atenolol or sotalol, alone or in combination with calcium antagonists ***(H. Yorgun, et al., 2008).***

This should not inhibit the slow, careful, titrated administration of beta-blockers later on, once patients are hemodynamically stable.

In patients with kidney dysfunction, undertreatment after myocardial infarction is common ***(A. Tessone, et al., 2007).***

Attention should be paid to preserving renal function, perhaps with the same vigor as we attempt to salvage and protect cardiac muscle. Worsening of renal function during admission for ST-segment elevation myocardial infarction is a powerful and independent predictor of in-

hospital and 1-year mortality ***(P. Jose, et al., 2006 and A. Goldberg, et al., 2005).***

In patients who receive percutaneous coronary intervention or cardiac surgery, even a small increase in serum creatinine (>0.3 mg/dl) is associated with increased hospital stay and mortality ***(A. Roghi, et al., 2008 and A. Lassnigg, et al., 2008).***

In this context, an increase in creatinine is not simply a marker of illness severity but, rather, it represents the onset of AKI acting as a causative factor for cardiovascular injury acceleration through the activation of neurohormonal, immunological and inflammatory pathways ***(T. Berl, et al., 2006 and H. Tokuyama, et al., 2007).***

No specific kidney-protective treatments have yet emerged for this condition. Despite some initial promising results, the use of nesiritide remains controversial, and a recent negative randomized controlled trial in these very patients suggests that this agent is unlikely to have significant clinical benefit. ***(R.M. Witteles, et al., 2007)***

A very specific and common threat to kidney function in the setting of acute cardiac disease relates to the administration of radiocontrast for heart imaging procedures. This topic, recently reviewed in the Journal would require separate detailed discussion and is beyond the scope of this article. Suffice it to say that this high-risk group requires appropriate prophylaxis to avoid radiocontrast nephropathy. Given that the presence of type 1 CRS defines a population with high mortality, a prompt, careful, systematic, multidisciplinary approach involving cardiologists, nephrologists, critical care physicians, and cardiac surgeons is both logical and desirable. ***(P.A. McCullough, 2008),***

In CRS type 1, the early diagnosis of AKI remains a challenge. This is also true in CRS type 3, where AKI is believed to be the primary inciting factor leading to cardiac dysfunction. ***(W.K. Han, et al., 2004).***

In both cases, classic markers such as creatinine increase when AKI is already established and very little can be done to prevent it or to protect the kidney. An interesting evolution in the early diagnosis of CRS has been the discovery of novel AKI biomarkers. With the use of a complementary deoxyribonucleic acid microarray as a screening technique, a subset of genes whose expression is up-regulated within the first few hours after renal injury has been discovered ***(P. Devarajan, et al., 2003 and M.T. Nguyen, et al., 2005).***

Neutrophil gelatinase-associated lipocalin (NGAL) appears to be one of the earliest markers detected in the blood and urine of humans with AKI ***(C. Ronco. 2008, S. Xu, et al., 2000 and J. Mishra, et al., 2003 and S. Supavekin, et al., 2003).***

Urine and serum NGAL are early predictors of AKI both in adult and children either in cardiac surgery or patients in the intensive care unit (ICU) **(K. Mori, et al., 2007 and J. Mishra, et al., 2005**).

In these patients, an increase in creatinine is observed only 48 to 72 h later. NGAL is also a biomarker of delayed graft function in kidney transplantation, ***(C.R. Parikh, et al., 2006).***

AKI caused by contrast-media**,** and AKI in critically ill patients admitted to intensive care ***(M. Zappitelli, et al., 2007).***

Cystatin C appears to be a better predictor of glomerular function than serum creatinine in patients with chronic kidney disease (CKD) because its blood levels are not affected by age, gender, race, or muscle mass ***(V.R. Dharnidharka, et al., 2002).***

Cystatin C predicts AKI and the requirement for renal replacement therapy earlier than creatinine ***(S. Herget-Rosenthal, et al., 2004).***

Serum cystatin C has been compared with NGAL in cardiac surgery-mediated AKI ***(R.G. VandeVoorde, et al., 2006).***

Both biomarkers predicted AKI at 12 h, although NGAL outperformed cystatin C at earlier time points. Considering them together, they may represent a combination of structural and functional damage of the kidney.

Kidney injury molecule 1 is a protein detectable in the urine after ischemic or nephrotoxic insults to proximal tubular cells and seems to be highly specific for ischemic AKI. Combined with NGAL which is highly sensitive, it may represent an important marker in the early phases of AKI. ***(W.K. Han, et al., 2002, T. Ichimura, et al., 2004 and V.S. Vaidya, et al., 2006)***

Biomarkers such as N-acetyl-β-(D) glucosaminidase interleukin (IL)-18 reported in Table 2 have been proposed as an interesting and promising contribution to diagnosis of AKI and progression of CKD. ***(O. Liangos, et al., 2007).***

The most likely evolution will be a “panel” of biomarkers that include several molecules both in serum and urine that combine their best characteristics in terms of specificity and sensitivity of each marker molecule.

Table 3.

Protein Biomarkers for the Early Detection of Acute Kidney Injury

Biomarker	Associated Injury
Cystatin C	Proximal tubule injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, pre-renal, post-renal AKI
Cytokines (IL-6, IL-8, IL-18)	Toxic, delayed graft function
Actin-actin depolymerizing F	Ischemia and delayed graft function
α-GST	Proximal T injury, acute rejection
π-GST	Distal tubule injury, acute rejection
L-FABP	Ischemia and nephrotoxins
Netrin-1	Ischemia and nephrotoxins, sepsis
Keratin-derived chemokine	Ischemia and delayed graft function

GST = glutathione S-transferase; IL = interleukin; KIM = kidney injury molecule; L-FABP = L-type fatty acid binding protein; NGAL = neutrophil gelatinase-associated lipocalin; NHE = sodium-hydrogen exchanger.

CRS type 2 (chronic CRS)

Type 2 CRS is characterized by chronic abnormalities in cardiac function (e.g., chronic congestive HF) causing progressive CKD (Fig. 2). Worsening renal function in the context of HF is associated with adverse outcomes and prolonged hospitalizations ***(P.A. McCullough, 2008).***

The prevalence of renal dysfunction in chronic HF has been reported to be approximately 25% ***(H.L. Hillege, et al., 2006).***

Even slight decreases in estimated glomerular filtration rate (GFR) significantly increase mortality risk and are considered a marker of severity of vascular disease. Independent predictors of worsening function include old age, hypertension, diabetes mellitus, and acute coronary syndromes. ***(R.S. Bhatia, et al., 2006).***

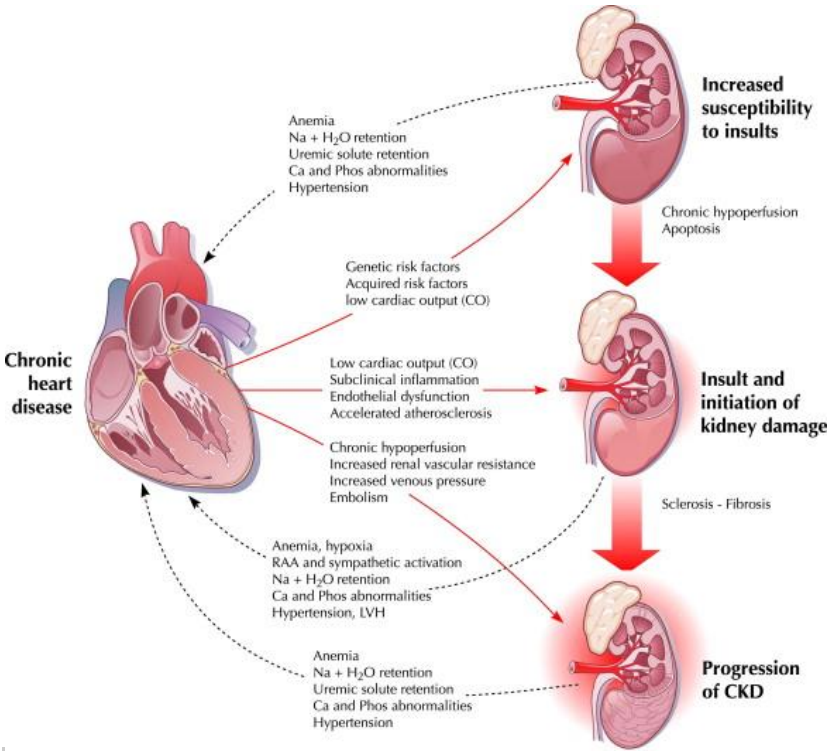


Figure 5.

CRS Type 2

Pathophysiological interactions between heart and kidney in type 2 cardiorenal syndrome (CRS) or "chronic CRS" (chronic abnormalities in cardiac function, e.g., chronic heart failure) causing progressive chronic kidney disease (CKD). Figure illustration by Rob Flewell. LVH = left ventricular hypertrophy; RAA = renin angiotensin aldosterone.

The mechanisms underlying worsening renal function likely differs based on acute versus chronic HF. Chronic HF is likely to be characterized by a long-term situation of reduced renal perfusion, often predisposed by microvascular and macrovascular disease. Although a greater proportion of patients with low estimated GFR have a worse New York Heart Association functional class, no evidence of association between LV ejection fraction and estimated GFR can be consistently demonstrated. Thus, patients with chronic HF and preserved LV function appear to have similar estimated GFR than patients with impaired LV (ejection fraction <45%) ***(R.S. Bhatia, et al., 2006).***

There is very limited understanding of the pathophysiology of renal dysfunction in the setting of even advanced cardiac failure. In this setting, where one would intuitively consider hemodynamic issues to be dominant, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Catheterization Effectiveness) trial found no link between any pulmonary artery catheter-measured hemodynamic variables and serum creatinine in 194 patients. The only link was with right atrial pressure, suggesting that renal congestion may be more important than appreciated. Clearly, hypoperfusion alone cannot explain renal dysfunction in this setting. More work needs to be performed to understand the mechanisms at play to develop targeted and physiologically sound approaches to treatment. ***(A. Nohria, et al., 2007)***

Neurohormonal abnormalities are present with excessive production of vasoconstrictive mediators (epinephrine, angiotensin, endothelin) and altered sensitivity and/or release of endogenous vasodilatory factors (natriuretic peptides, nitric oxide). Pharmacotherapies used in the management of HF may worsen renal function. Diuresis-associated hypovolemia, early introduction of renin-angiotensin-aldosterone system blockade, and drug-induced hypotension have all been suggested as contributing factors ***(K.V. Liang, et al., 2008).***

More recently, there has been increasing interest in the pathogenic role of relative or absolute erythropoietin deficiency contributing to a more pronounced anemia in these patients than might be expected for renal failure alone ***(K.E. Jie, et al., 2006).***

Erythropoietin receptor activation in the heart may protect it from apoptosis, fibrosis, and inflammation ***(P. Fu, M.O. Arcasoy 2007 and N.P. Riksen, et al., 2008).***

Preliminary clinical studies show that erythropoiesis-stimulating agents in patients with chronic HF, CKD, and anemia lead to improved cardiac function, reduction in LV size, and the lowering of B-type natriuretic peptide (BNP) ***(A. Palazzuoli, et al., 2007).***

Patients with type 2 CRS are more likely to receive loop diuretics and vasodilators and also to receive greater doses of such drugs compared with those patients with stable renal function ***(J. Butler, et al., 2004).***

Treatment with these drugs may participate in the development and progression of renal injury. However, such therapies may simply identify patients with severe hemodynamic compromise and, thus, a predisposition to renal dysfunction rather than being responsible for worsening function.

CRS type 3 (acute renocardiac syndrome)

Type 3 CRS is characterized by an abrupt and primary worsening of kidney function (e.g., AKI, ischemia, or glomerulonephritis), leading to acute cardiac dysfunction (e.g., HF, arrhythmia, ischemia). Type 3 CRS appears less common than type 1 CRS, but this may only be due to the fact that, unlike type 1 CRS, it has not been systematically studied. AKI is a growing disorder in hospital and ICU patients. When the RIFLE (risk, injury, and failure; loss; and end-stage kidney disease) consensus definition is used, AKI has been identified in close to 9% of hospital patients ***(S. Uchino, et al., 2006).***

In a large ICU database, AKI was observed in more than 35% of patients ***(S.M. Bagshaw, et al., 2008).***

Acute kidney injury can affect the heart through several pathways (Fig. 3), whose hierarchy is not yet established. Fluid overload can contribute to the development of pulmonary edema. Hyperkalemia can contribute to arrhythmias and may cause cardiac arrest. Untreated uremia affects myocardial contractility through the accumulation of myocardial depressant factors and pericarditis ***(T.W. Meyer, et al., 2007).***

Acidemia produces pulmonary vasoconstriction**,** which can significantly contribute to right-sided HF. Acidemia appears to have a negative inotropic effect and might, together with electrolyte imbalances, contribute to an increased risk of arrhythmias ***(P.A. McCullough, et al., 2004).***

Finally, renal ischemia itself may precipitate activation of inflammation and apoptosis at cardiac level ***(T. Berl, et al,. 2006).***

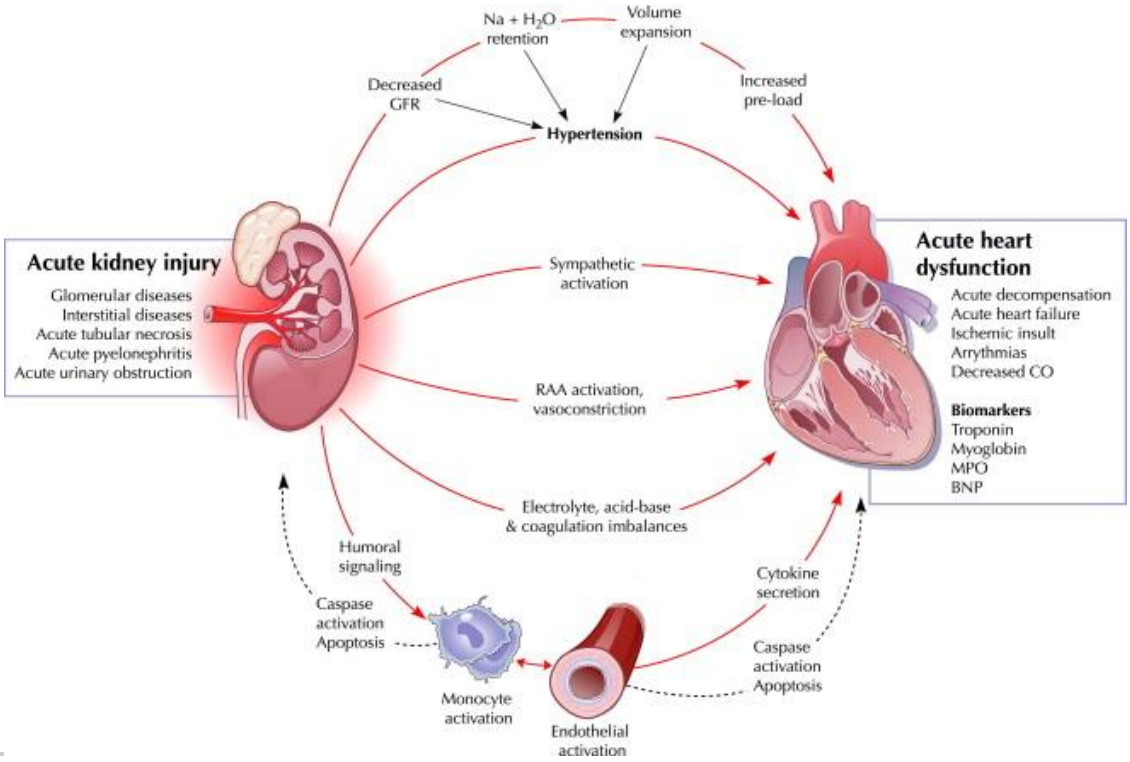


Figure 6.

CRS Type 3

Pathophysiological interactions between heart and kidney in type 3 CRS or "acute renocardiac syndrome" (abrupt worsening of renal function, e.g., acute kidney failure or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, pulmonary edema). MPO = myeloperoxidase; other abbreviations as in Figure 1. Figure illustration by Rob Flewell.

A unique situation leading to type 3 CRS is bilateral renal artery stenosis (or unilateral stenosis in a solitary kidney). Patients with this condition may be prone to acute or decompensated HF because of diastolic dysfunction related to chronic increase of blood pressure from excessive activation of the renin-angiotensin-aldosterone axis, renal dysfunction with sodium and water retention, and acute myocardial ischemia from an increase in myocardial oxygen demand related to intense peripheral vasoconstriction ***(S.K. Gandhi, et al., 2001 and A.T. Hirsch, et al., 2006).***

In these patients, angiotensin blockade is generally required to manage the hypertension and HF. However, the GFR is highly dependent upon angiotensin and significant decompensation of kidney function may ensue. Although the management of these unusual patients has not been subject to scrutiny in large randomized trials, those exhibiting renal decompensation with ACE inhibition or ARB are likely candidates for renal revascularization ***(A.T. Hirsch, et al., 2006).***

Sensitive and specific biomarkers of cardiac injury may help physicians to diagnose and treat type 3 CRS earlier and perhaps more effectively ***(S.V. Parikh, et al., 2006).***

Cardiac troponins are biomarkers for ischemic myocardial injury**,** and they correlate with outcomes in the general population and specifically in renal patients ***(D.S. Ooi, et al., 1999, D.M. Needham, et al., 2004 and C. Sommerer, et al., 2007).***

A marker of myocyte stress is BNP and allows the diagnosis of acute and acutely decompensated chronic HF ***(A. Maisel, et al., 2004).***

It also is an independent predictor of cardiovascular events and overall mortality in the general population and also in patients with renal insufficiency ***(S.J. Carr, et al., 2005, W.J. Austin, et al., 2006, and M. Suresh, et al., 2005).***

In HF, despite high levels of serum BNP, its physiological effects (vasodilatory, diuretic, and natriuretic) do not appear sufficient to prevent the disease progression and CRS. Recent findings suggest a resistance to BNP and/or a relative preponderance of the biologically inactive precursor of BNP ***(F. Liang, et al., 2007).***

In CRS type 4, an association between increased levels of BNP and the accelerated progression of nondiabetic CKD to end-stage kidney disease has been observed ***(K.S. Spanaus, et al., 2007).***

Myeloperoxidase is a marker of altered myocyte metabolism, oxidative stress, and inflammation, especially in acute coronary syndrome ***(V. Loria, et al., 2008).***

Oxidative stress may cause myocyte apoptosis and necrosis, and it is associated with arrhythmias and endothelial dysfunction with a potential role in the pathogenesis of CRS ***(E. Braunwald, 2008).***

Cytokines such as tumor necrosis factor (TNF), IL-1, and IL-6 may have a diagnostic role as early biomarkers of CRS, but also a pathogenic role causing myocardial cell injury and apoptosis and mediating myocardial damage in ischemic AKI ***(K.J. Kelly, et al., 2003).***

The development of AKI can affect the use of medications normally prescribed in patients with chronic HF. For example, an increase in serum creatinine from 1.5 mg/dl (130 μmol/l) to 2 mg/dl (177 μmol/l), with diuretic therapy and ACE inhibitors, may provoke some clinicians to decrease or even stop diuretic prescription; they may also decrease or even temporarily stop ACE inhibitors. This may, in some cases, lead to acute decompensation of HF. It should be remembered that ACE inhibitors do not damage the kidney but rather modify intrarenal hemodynamics and reduce filtration fraction. They protect the kidney by reducing pathological hyperfiltration. Unless renal function fails to stabilize, or other dangerous situations arise (i.e., hypotension, hyperkalemia) continued treatment with ACE inhibitors and ARBs may be feasible.

Finally, if AKI is severe and renal replacement therapy is necessary, cardiovascular instability generated by rapid fluid and electrolyte shifts secondary to conventional dialysis can induce hypotension, arrhythmias, and myocardial ischemia ***(N.M. Selby, et al., 2007).***

Continuous techniques of renal replacement, which minimize such cardiovascular instability, appear physiologically safer and more logical in this setting ***(C. Ronco, et al., 2001).***

CRS type 4 (chronic renocardiac syndrome)

Type 4 CRS is characterized by a condition of primary CKD (e.g., chronic glomerular disease) contributing to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events (Fig. 4). Today, CKD is divided into 5 stages based on a combination of severity of kidney damage and GFR ***(National Kidney Foundation, et al., 2002).***

When these criteria are used, current estimates of CKD account for at least 11% of the U.S. adult population thus becoming a major public health problem. In fact CKD today includes individuals with serum creatinine levels previously dismissed as not representative of significant renal dysfunction. ***(J. Coresh, et al., 2003),***

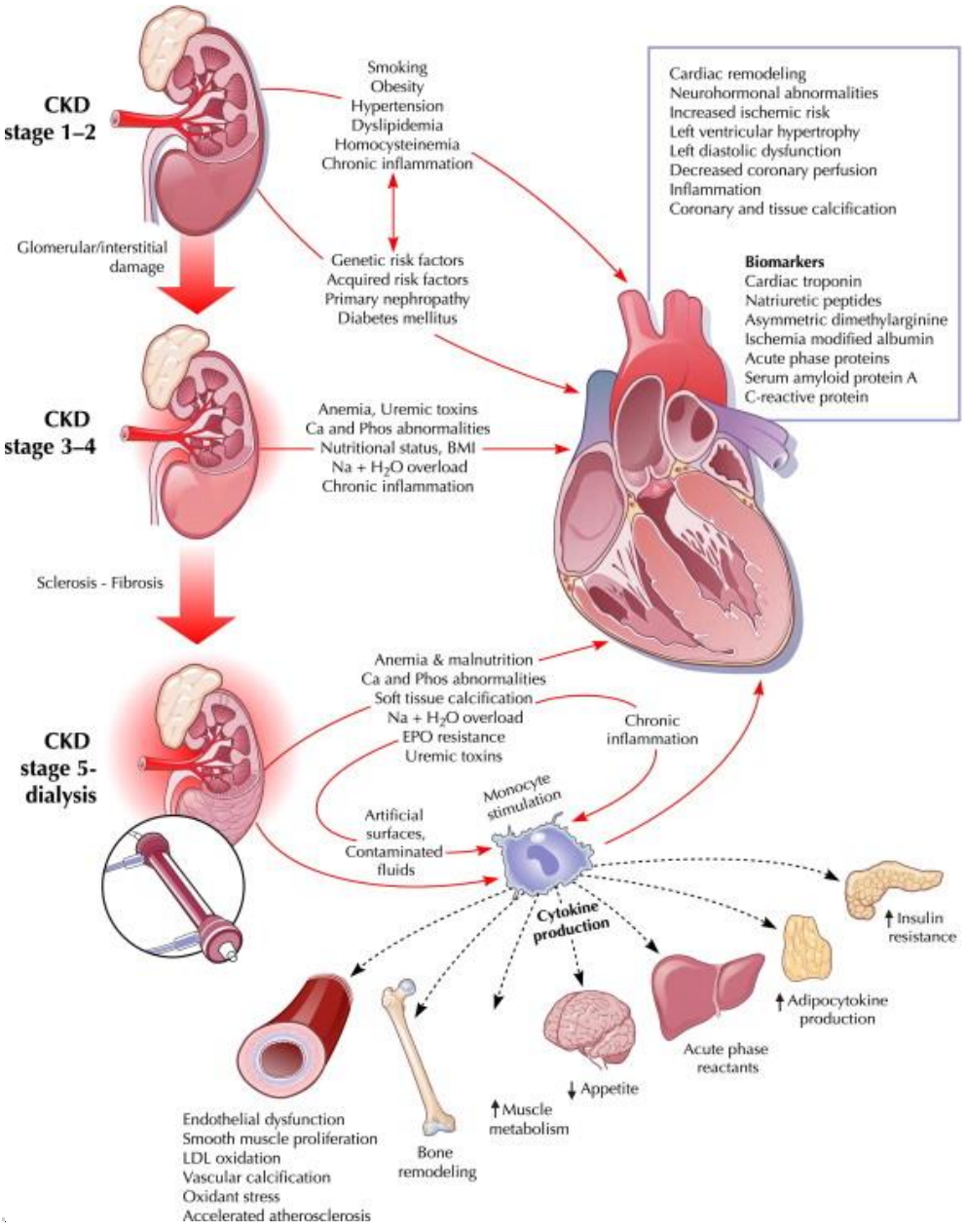


Figure 7.

CRS Type 4

Pathophysiological interactions between heart and kidney in type 4 cardiorenal syndrome (CRS) or “chronic renocardiac syndrome” (chronic kidney disease [CKD], e.g., chronic glomerular disease, contributing to decreased cardiac function, cardiac hypertrophy, or increased risk of adverse cardiovascular events). BMI = body mass index; EPO = erythropoietin; LDL = low-density lipoprotein. Figure illustration by Rob Flewell.

Individuals with CKD are at extremely high cardiovascular risk. More than 50% of deaths in CKD stage 5 cohorts are attributed to cardiovascular disease. The 2-year mortality rate after myocardial infarction in patients with CKD stage 5 is estimated to be 50% ***(C.A. Herzog, et al., 2002).***

In comparison, the 10-year mortality rate post-infarct for the general population is 25%. Patients with CKD have between a 10- and 20-fold increased risk of cardiac death compared with age-/gender-matched control subjects without CKD ***(C.A. Herzog, et al., 2002, D.W. Johnson, et al., 2007 and C.M. Logar, et al., 2003).***

Part of this problem may be related to the fact that such individuals are also less likely to receive risk-modifying interventions compared to their non-CKD counterparts ***(A.J. Collins, et al., 2003).***

Less severe forms of CKD also may be associated with significant cardiovascular risk. Evidence for increasing cardiovascular disease morbidity and mortality tracking with mild-to-moderate renal dysfunction (stages 1 to 3) has mainly stemmed from community-based studies ***(A.S. Go, et al., 2004, A.X. Garg, et al., 2002, D.S. Keith, et al., 2004 and M.J. Sarnak, 2002).***

These studies documented an inverse relationship between renal function and adverse cardiovascular outcomes (consistently occurring at estimated GFR levels <60 ml/min/1.73 m^2).

Among high-risk cohorts, baseline creatinine clearance is a significant and independent predictor of short-term outcomes, namely death and myocardial infarction ***(D.W. Johnson, et al., 2007).***

Similar findings also were noted among patients presenting with ST-segment elevation myocardial infarction, an effect independent of the Thrombolysis In Myocardial Infarction risk score ***(C.M. Gibson, et al., 2003).***

In large-scale studies (e.g., SOLVD [Studies Of Left Ventricular Dysfunction], TRACE [Trandolapril Cardiac Evaluation], SAVE [Survival And Ventricular Enlargement], and VALIANT [Valsartan in Acute Myocardial Infarction]) in which the authors excluded individuals with baseline serum creatinine of ≥2.5 mg/dl, reduced renal function was associated with significantly greater mortality and adverse cardiovascular event rates ***(A. Al-Ahmad, et al., 2001, C.R. Sorensen, et al., 2002, M.P. Tokmakova, et al., 2004 and N.S. Anavekar, et al., 2004).***

Adverse cardiovascular outcomes in renal patients are associated with plasma levels of specific biomarkers**.** Troponins, asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, natriuretic peptides, C-reactive protein, serum amyloid A protein, hemoglobin, and ischemia-modified albumin are biomarkers whose levels correlate with cardiovascular outcomes in patients with CKD. ***(M. Rattazzi, et al., 2003, G. Liuzzo, et al., 1994 and V. Panichi, et al., 2004).***

These observations provide a mechanistic link between chronic inflammation, subclinical infections, accelerated atherosclerosis, heart–kidney interactions, and negative cardiovascular and renal outcomes.

The proportion of individuals with CKD receiving appropriate cardiovascular risk modification treatment is lower than in the general population. This "therapeutic nihilism"**,** is based on the concern of worsening kidney function and leads to treating <50% of patients with

CKD with the combination of aspirin, beta-blockers, ACE inhibitors, and statins ***(A.K. Berger, et al., 2003).***

In a cohort involving >140,000 patients, 1,025 with documented CKD were less likely to receive aspirin, beta-blockade, or ACE inhibition after infarction than patients without CKD. Yet CKD patients had 30-day mortality risk reductions similar to non-CKD patients when receiving the drug combination ***(A.K. Berger, et al., 2003).***

Potential reasons for this subtherapeutic performance include concerns about further worsening of renal function, and/or therapy-related toxic effects due to low clearance rates ***(W.J. French, et al., 2003).***

Many medications necessary for management of complications of advanced CKD generally are considered safe with concomitant cardiac disease. These include regimens for calcium-phosphate balance and hyperparathyroidism, vitamins, and erythropoiesis-stimulating agents ***(W.N. Suki, et al., 2007).***

The same appears to hold true for novel regimens, for instance, endothelin system antagonists, adenosine and vasopressin receptor antagonists, and inflammation suppressors ***(W. Neuhofer, et al., 2006).***

For immunosuppressive drugs, controversy exists regarding the effects of certain agents on the heart, indicating a need for more research in the area ***(Y. Sakata, et al., 2000).***

Bleeding concerns contribute to the decreased likelihood of patients with severe CKD receiving aspirin and/or clopidogrel despite the minor bleeding risk and benefits that are sustained in these patients ***(M. Keltai, et al., 2007).***

Other medications requiring thorough considerations of pros and cons include diuretics, digitalis, calcium-channel blockers, and nesiritide ***(W.Y. Sun, et al., 2006).***

Nevertheless, when appropriately titrated and monitored, cardiovascular medications can be safely administered to CKD patients with benefits similar to the general population ***(P. Ruggenenti, et al., 2001).***

Lack of CKD population-specific treatment effect data makes therapeutic choices particularly challenging. In particular, in patients with advanced CKD, the initiation or increased dosage of ACE inhibitors or ARBs can precipitate clinically significant worsening of renal function or marked hyperkalemia. The latter may be dangerously exacerbated by the use of aldosterone antagonists. Such patients, if aggressively treated, become exposed to a significant risk of developing dialysis dependence or life-threatening hyperkalemic arrhythmias. Yet, if too cautiously treated, they may develop equally life-threatening cardiovascular complications.

It is comforting to note that up to a 30% increase in creatinine that stabilizes within 2 months was actually associated with long-term nephroprotection in a systematic review of 12 randomized controlled studies ***(G.L. Bakris, et al., 2000).***

This result leads to the practical advice that ACE inhibitors and ARBs can be cautiously used in patients with CKD, provided the serum creatinine does not increase beyond this amount and potassium remains consistently <5.6 mmol/l. Regarding patients with end-stage renal disease, and in particular those with anuria and a tendency to hyperkalemia interdialytically, the administration of ACE inhibitors or ARBs may be problematic; however, even the combination of these medications has been used safely in select populations ***(S.W. Han, et al., 2007).***

At present, most end-stage kidney disease patients with LV dysfunction seem to be undertreated with ACE inhibitors or ARBs ***(P. Roy, et al., 2006).***

With respect to aldosterone blockade, drugs such as spironolactone have been widely used for severe HF patients with evidence of beneficial effects on morbidity and mortality ***(M. Jessup, 2003).***

Concerns have been raised, however, about the use of aldosterone blockade, particularly in conjunction with angiotensin blockade, since after publication of RALES (Randomized Aldactone Evaluation Study, prescriptions for spironolactone and rates of hospitalizations and mortality related to hyperkalemia increased sharply ***(D.N. Juurlink, 2004).***

Proper patient selection, including patients with diminished LV ejection fraction and excluding ones with moderate CKD (creatinine level ≥2.5 mg/dl) or hyperkalemia >5 mmol/l, would help minimize potential life-threatening hyperkalemia ***(D.T. Ko, et al., 2006).***

CRS type 5 (secondary CRS)

Type 5 CRS is characterized by the presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders (Fig. 5). There is limited systematic information on type 5 CRS, although there is an appreciation that as more organs fail in this setting, mortality increases. There is limited insight into how combined renal and cardiovascular failure may differentially affect such an outcome compared to, for example, combined pulmonary and renal failure. Nonetheless, it is clear that several acute and chronic diseases can affect both organs simultaneously and that the disease induced in one can affect the other and vice versa. Examples include sepsis, diabetes, amyloidosis, systemic lupus erythematosus, and

sarcoidosis. Several chronic conditions such as diabetes and hypertension may contribute to type 2 and 4 CRS.

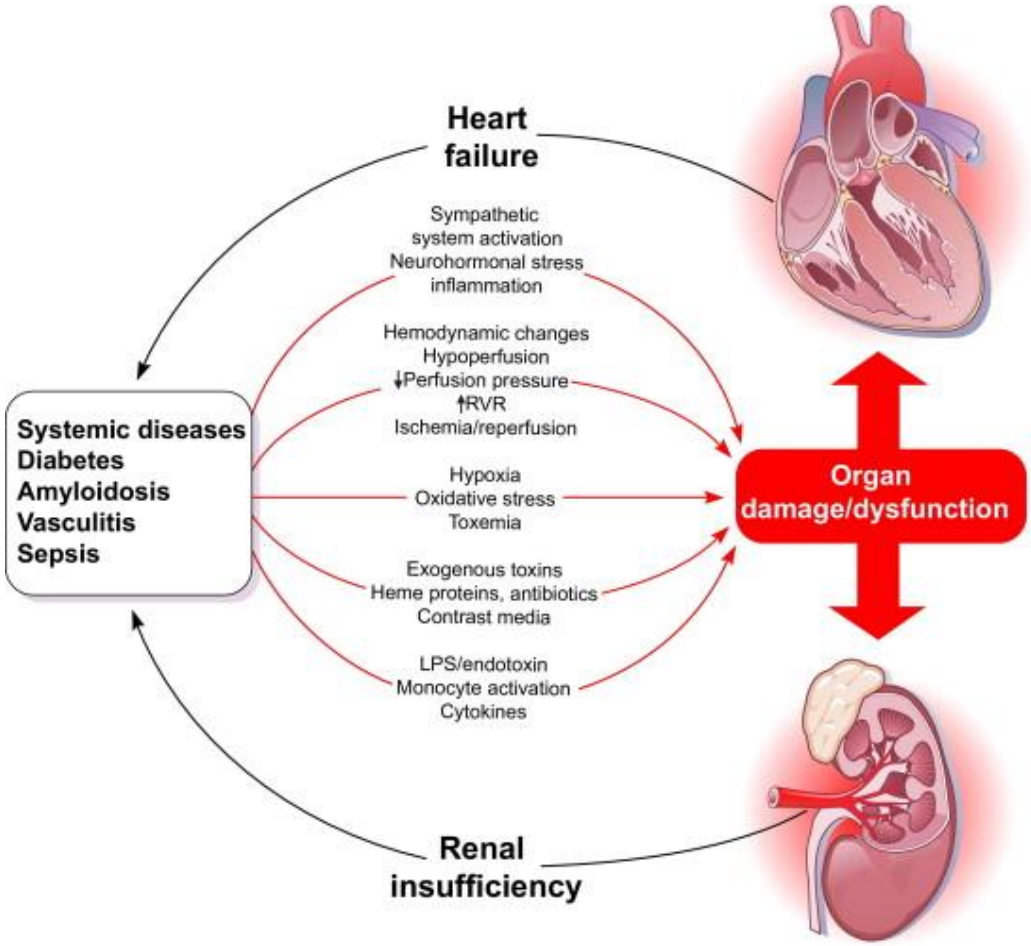


Figure 8.

CRS Type 5

Pathophysiological interactions between heart and kidney in type 5 cardiorenal syndrome (CRS) or "secondary CRS" (systemic condition, e.g., diabetes mellitus, sepsis, causing both cardiac and renal dysfunction). LPS = lipopolysaccharide (endotoxin); RVR = renal vascular resistance. Figure illustration by Rob Flewell.

In the acute setting, severe sepsis represents the most common and serious condition which can affect both organs. It can induce AKI while

leading to profound myocardial depression. The mechanisms responsible for such changes are poorly understood but may involve the effect of TNF and other mediators on both organs ***(P.N. Cunningham, et al., 2002).***

The onset of myocardial functional depression and a state of inadequate cardiac output can further decrease renal function as discussed in type 1 CRS, and the development of AKI can affect cardiac function as described in type 3 CRS. Renal ischemia may then induce further myocardial injury in a vicious cycle, which is injurious to both organs. Treatment is directed at the prompt identification, eradication, and treatment of the source of infection while supporting organ function with invasively guided fluid resuscitation in addition to inotropic and vasopressor drug support***. (A. Kumar, et al., 2007)***

In this setting, all the principles discussed for type 1 and 3 CRS apply. In these septic patients, preliminary data derived from the use of more intensive renal replacement technology suggest that blood purification may have a role in improving myocardial performance while providing optimal small solute clearance ***(P.M. Honore, et al., 2000).***

Despite the emergence of consensus definitions and many studies, no therapies have yet emerged to prevent or attenuate AKI in critically ill patients. However, evidence of the injurious effects of pentastarch fluid resuscitation in septic AKI recently has emerged. Such therapy should, therefore, be avoided in septic patients. ***(F.M. Brunkhorst, et al., 2008)***

Management of Acute Cardio-renal Syndrome

Specific treatment is designed to ameliorate decreased urine output, decreased glomerular filtration rate, increased serum creatinine, and to prevent weight loss. Current pharmacologic management consists of inotropic agents and vasodilators in the majority of cases, and also includes neurohormonal antagonists and diuretics. Such as vasopressin antagonists, adenosine antagonists, and natriuretic peptides, have potentially therapeutic value, although to date, the results of clinical studies using these treatments have been disappointing.

Inotropic Agents and Low-dose Dopamine

Inotropic agents are widely used to treat patients with low blood pressure and poor cardiac output. Drugs such as dobutamine and milrinone improve cardiac index in proportion with renal blood flow, but these improvements are not clearly associated with better clinical outcome or reduced mortality.

The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of a Chronic Heart Failure (OPTIME-HF) trial reported that milrinone did not improve kidney function or overall survival in acute decompensated heart failure (ADHF) patients ***(Klein L, Massie BM, et al., 2008).***

Low-dose dopamine (<5 μg·min-1·kg-1), commonly combined with diuretics, is believed to increase renal vasodilatation and renal blood flow, attenuate the effects of norepinephrine and aldosterone, and promote natriuresis via effects on dopamine-1 and 2 receptors ***(Marik PE. 2002).***

A prospective, double-blind, randomized, controlled study concluded that low-dose dopamine can worsen renal perfusion in patients with acute

renal failure, supporting a trend to abandon the routine use of low-dose dopamine in critically ill patients ***(Lauschke A. el al., 2006).***

The Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial found that the combination of low-dose furosemide and low-dose dopamine is equally effective as high-dose furosemide and is also associated with improved renal function and potassium homeostasis ***(Giamouzis G. et al., 2010).***

Therefore, treatment with low-dose dopamine could be useful for CRS patients who require high-dose furosemide. A small randomized trial of levosimendan, a calcium sensitizing phosphodiesterase inhibitor, involving patients with heart failure showed an increase of 45.5% in estimated glomerular filtration rate (GFR) at 72 hours in the levosimendan group versus 0.1% GFR increase in those treated with dobutamine**http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3741438/ - B10** ***(Giamouzis G. et al., 2010).***

Diuretics and Vasodilators

Diuretics and vasodilators play an important role in the early management of CRS and its complications of venous hypertension, increased intra-abdominal pressure, and renal congestion. However, in high doses, diuretics may aggravate electrolyte disturbances, decrease the effective circulating volume, disturb neurohormonal balance, and lead to decreased kidney function. Since both heart failure and renal dysfunction frequently require high-dose diuretic treatment, the administered dose must be carefully calculated to improve fluid balance and relieve symptoms without stimulating adverse physiologic effects. ***(Mullens W. et al., 2009)***

Vasodilators can rapidly decrease ventricular filling pressures and central venous pressure, thereby reducing myocardial oxygen consumption and relieving pulmonary congestion. Intravenous nitroglycerine, a vasodilator commonly used to treat ADHF, may also reduce trans-renal

perfusion pressure by decreasing venous pressure ***(den Uil CA, Lagrand WK, et al. 2009)***.

However, it is not clear whether the effect of nitroglycerine improved kidney function or long-term survival. Sodium nitroprusside produces significant arterial and venous vasodilatation through its action on cyclic guanosine monophosphate in vascular smooth muscle. In a nonrandomized trial, ADHF patients treated with sodium nitroprusside experienced favorable long-term clinical outcomes irrespective of inotropic support or kidney dysfunction ***(Mullens W. et al., 2008).***

However, thiocyanate accumulation is a dangerous potential side effect in patients with decreased kidney function.

Nesiritide, a recombinant form of human B-type natriuretic peptide, produces venous, arterial, and coronary vasodilatation, decreasing the cardiac preload and afterload and increasing cardiac output without direct inotropic effects. Investigations involving the safety and physiologic effects of nesiritide show mixed results. In one study of ADHF patients, nesiritide significantly increased the risk of worsening renal function, even at low doses (≤0.015 μg·kg-1·min-1) ***(Sackner-Bernstein JD, et al., 2005).***

Nevertheless, subsequent studies suggested that this drug could still potentially be used in renal-protective therapy in ADHF, with appropriate doses (0.01 μg·kg-1·min-1) ***(Witteles RM, et al., 2007, Yancy CW, et al., 2008).***

The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) showed that nesiritide was not associated with a change in the rate of death and re-hospitalization, and had no unfavorable effects on kidney function compared with a placebo. Nesiritide may not be recommended for routine use in most patients with acute heart failure, it could be used for short-term treatment in patients

resistant to commonly prescribed drugs such as diuretics and vasodilators ***(O'Connor CM, et al., 2011).***

Vasopressin and Adenosine Antagonists

Selective vasopressin V2 antagonists, such as tolvaptan and conivaptan, can facilitate free water clearance, and increase the serum sodium level without disturbing plasma potassium and magnesium levels ***(Lemmens-Gruber R, et al., 2006).***

The Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial investigated 4,133 patients with ADHF and found that early administration of tolvaptan was associated with decreased mean body weight and improved dyspnea. Although comparison of tolvaptan and placebo groups showed no difference in long-term outcomes ***(Konstam MA, et al., 2007).***

Drugs that selectively block adenosine A1-receptors and preserve adenosine A2-receptor activity can increase urine output while maintaining kidney function. Patients who received rolofylline, a selective A1 receptor antagonist, showed a persistent increase in urine output without a decline in kidney function ***(Givertz MM, et al., 2007).***

However, the PROTECT trial failed to demonstrate any functional benefit or improvement in outcome including death or re-hospitalization for cardiovascular or renal disease. Similarly, the REACH-UP trial-a multicenter, international, randomized, double-blind, placebo-controlled study of patients with ADHF-showed no clear beneficial effect of rolofylline on the clinical status and recent or acute worsening of renal function ***(Gottlieb SS, et al., 2010).***

In conclusion, the efficacy of adenosine A1-receptor antagonists for treatment of CRS is still undecided and larger clinical trials are needed to resolve this issue.

Management of Chronic Cardio-renal Syndrome

RAAS blockade

RAAS inhibitors have been shown to reduce mortality in patients with cardiac failure, although the majority of these studies excluded patients with significant renal impairment ***(Shlipak MG. 2003).***

These drugs also prevent progression of renal insufficiency in diabetic nephropathy and other forms of chronic kidney disease. The Cooperative North Scandinavian Enalapril ***(Ljungman S, et al., 1992)*** of patients with severe heart failure included individuals with renal dysfunction whose serum creatinine concentrations did not exceed 3.4mg/dL. The subgroup of patients with serum creatinine levels higher than 2mg/dL exhibited an improvement in outcomes when treated with an angiotensin-converting enzyme (ACE) inhibitor. The ACE inhibitors or angiotensin II-receptor blockers (ARB) should be used cautiously in patients with CRS, considering the associated risks of hyperkalemia and transient increase in creatinine levels. The patients should be started on the lowest dose of RAAS blockers and kidney function should be closely monitored during initiation and up-titration in order to reduce the incidence of renal deterioration; this is especially important for dehydrated patients. Moreover, concomitant use of NSAIDs should be avoided ***(Shlipak MG. 2003).***

Spironolactone and eplerenone decrease morbidity and mortality in patients who develop heart failure after acute myocardial infarction. The RALES and EPHESUS trials demonstrated that, in patients already receiving standard medications for heart failure, adding low-dose spironolactone or eplerenone dramatically improved the outcome. Although several studies confirm that mineralocorticoid receptor antagonists have organ protective effects, patients with renal dysfunction

are at greater risk of hyperkalemia. Thus, the long-term effects of mineralocorticoid receptor antagonists on renal outcome, mortality, and safety in patients with CRS requires further study. ***(Pitt B, Zannad F, et al., 1999, Pitt B, Remme W, et al., 2003)***

β-blockers

Activation of the sympathetic nervous system is a common occurrence in cardiac and renal failure. Interrupting this response is important to preventing progression of cardiovascular and renal disease. The β-blocker carvedilol has favorable effects on renal function in select patients with heart and kidney disease, and may offer a benefit over older formulations of β-blockers. However, large randomized clinical trials on β-blocker treatment in heart failure excluded patients with severe renal dysfunction and did not consider their effects on renal outcome. ***(Bakris GL, et al., 2006).***

Antithrombotic therapy

Although aspirin can potentially interfere with GFR through its actions on cyclooxygenase and renal prostaglandins, aspirin in low doses has long been considered safe for use in patients with kidney disease. This was confirmed in the first UK Heart and Renal Protection Study**,** which showed that low-dose aspirin (100mg/d) did not significantly impair kidney function or increase the risk for renal replacement therapy, nor did it substantially increase the risk for major bleeding even in patients with risk factors for minor bleeding. ***(Baigent C, et al., 2005)***

The efficacy of other antithrombotic agents, such as clopidogrel and low-molecular weight heparins, in patients with decreased renal function is uncertain and needs further investigation ***(Keltai M, et al., 2007, Best PJ, et al., 2008).***

Anemia management

Anemia is present in over one-third of CRS patients ***(Silva RP, et al., 2007)***.

Cardio-renal anemia syndrome (CRAS) refers to the simultaneous presence of anemia, heart failure, and renal failure, forming a pathologic triad that adversely impacts morbidity and mortality ***(Kazory A, et al., 2009)***.

There is no consensus over the definition, significance, and management of CRAS. The role of erythropoiesis-stimulation agents (ESAs) in the treatment of CRAS is particularly controversial. Elevated serum erythropoietin is an adverse predictor of morbidity and mortality in heart failure ***(George J, et al., 2005, van der Meer P, et al., 2008).***

However, erythropoietin receptor activation in the heart may be protective for apoptosis, fibrosis, and inflammation, providing a rationale for using ESAs in patients with heart failure ***(Silverberg DS, et al., 2006).***

A randomized double-blind controlled study showed that the correction of anemia with erythropoietin and oral iron over 1 year led to improvements in cardiac function, left ventricular remodeling, and B-type natriuretic peptide levels compared with oral iron therapy alone ***(Palazzuoli A, et al., 2007).***

There is also increasing interest in the use of parenteral iron to correct anemia in patients with congestive heart failure. Two recent trials, FERRIC-HF and FAIR-HF, demonstrated that patients treated with intravenous iron showed symptomatic improvement and increased exercise capacity independent of the effects on hemoglobin level. This data suggests that intravenous iron therapy is a potential option for the treatment of CRAS. ***(Okonko DO, et al., 2008, Anker SD, et al., 2009)***

Epidemiology and Outcomes in Combined Cardiorenal Disease: The Scope of the Problem

Prevalence of Renal Disease in Patients With HF

In the Acute Decompensated Heart Failure National Registry (ADHERE) of >105 000 individuals admitted for acute decompensated HF, 30% had a history of renal insufficiency, 21% had serum creatinine concentrations >2.0 mg/dL, and 9% had creatinine concentrations >3.0 mg/dL. McAlister et al found that only 17% of 754 outpatients with HF had creatinine clearances >90 mL/min. 39% with New York Heart Association (NYHA) class IV symptoms and 31% with NYHA class III symptoms had creatinine clearance <30 mL/min. These numbers are striking when one considers the complexity of treating volume overload in those with coexistent renal disease and that there are >1 million hospital admissions for decompensated HF in the United States annually. ***(McAlister FA, et al., 2003)***

Impact of Renal Disease on Clinical Outcomes in Patients with HF

Renal dysfunction is one of the most important independent risk factors for poor outcomes and all-cause mortality in patients with HF. Baseline glomerular filtration rate (GFR) appears to be a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class. Both elevated serum creatinine on admission and worsening creatinine during hospitalization predict prolonged hospitalization, rehospitalization, and death. ***(Hillege HL, et al., 2000).***[**http://www.circ.ahajournals.org/content/121/23/2592.full - ref-6**](http://www.circ.ahajournals.org/content/121/23/2592.full - ref-6)

Even small changes in creatinine <0.3 mg/dL are common and have been associated with increased mortality and prolonged hospitalization. ***(Gottlieb SS, et al., 2002).***

The frequency and time course of developing an increase in creatinine in patients hospitalized with HF. The percent of patients with an increase (by that time in the hospitalization) in creatinine of at least the value indicated is shown. Worsening renal function is common in patients with HF. Reprinted from Gottlieb et al. ***(Gottlieb SS, et al., 2002).***

HF Outcomes in Patients with Renal Disease

On the basis of estimates provided by the Third National Health and Nutrition Examination Survey (NHANES III), almost 8 million individuals living in the United States have a GFR <60 mL/min. ***(Coresh J, et al., 2003).***

Patients with chronic renal insufficiency are at strikingly higher risk for myocardial infarction, HF with systolic dysfunction, HF with preserved left ventricular ejection fraction, and death resulting from cardiac causes compared with individuals with normal GFR. ***(Foley RN, et al., 1998).***

A recent meta-analysis suggests that individuals with primary renal disease are more likely to eventually die of cardiovascular causes than renal failure itself. ***(Tonelli M, et al., 2006)***.

This is not just secondary to atherosclerotic disease; in a multicenter cohort study of 432 patients, 31% planning to initiate hemodialysis had HF symptoms, and 33% of such patients had estimated left ventricular ejection fraction <40%. ***(Harnett JD, et al., 1995).***

Patients with HF and new hemodialysis had a median survival of only 36 months compared with 62 months in patients without HF. Furthermore, 25% who did not have HF symptoms on initiation of dialysis developed these symptoms after a median follow-up of 15 months. Conversely, reversal of renal dysfunction can improve cardiac function. In

a study of 103 hemodialysis patients with HF and left ventricular ejection fraction <40%, the mean ejection fraction increased from 32% to 52% after renal transplantation, and 70% had normalization of cardiac function. ***(Wali RK, et al., 2005).***

Hypertensive heart disease and HF with a normal ejection fraction are common among individuals with advanced and end-stage renal disease. One study showed that there is echocardiographic evidence of left ventricular hypertrophy in 45% of individuals with creatinine clearance <24 mL/min and in 70% of those planning to initiate hemodialysis. ***(Levin A, et al., 1996)***.

Renal disease patients with left ventricular hypertrophy have accelerated rates of coronary events and markers of uremia compared with those with normal left ventricular mass, and a high proportion of these individuals develop clinical HF. ***(Parfrey PS, et al., 1996).***

Traditional and Emerging Hypotheses for the Pathophysiology of Cardiorenal Failure

Evolutionary mechanisms designed to maintain constant blood volume and organ perfusion under continuously changing conditions are clearly responsible for CRS. Unfortunately, when primary cardiac or renal dysfunction develops, the renin-angiotensin-aldosterone system (RAAS), pressure-sensing baroreceptors, cellular signaling, and sympathetic nervous system mechanisms turn from friend to foe. Attempting to understand the nature of these normal physiological mechanisms gone away is a key to developing a multimodal approach to preserving function in both organs. ***(Mullens W, et al., 2008)***

The Low-Flow-State Hypothesis

Traditional reasoning held that the progressive decline in GFR observed in HF primarily reflects inadequate renal perfusion secondary to reduced cardiac output. Many surmised that inadequate renal blood flow or perfusion pressure prompts renin release by the juxtaglomerular cells of the afferent arterioles through low-flow states in the ascending limb of the loop of Henle and pressure-sensing baroreceptors. Renin release and RAAS activation confer extreme sodium avidity, volume retention, decreased glomerular perfusion (ie, afferent arteriolar constriction), and profibrotic neurohormone increases, leading to ventricular remodeling. On one hand, this reasoning is not incorrect because all of the above conditions are observed in HF (neurohormonal stimulation, decreased fractional excretion of sodium, myocardial fibrosis). Experience would also suggest that, by augmenting contractility, heart rate, and cardiac index, inotropes can lead to short-term improvement in urine output, mental status, and other clinical indicators of organ perfusion. However, recent investigations suggest that this viewpoint is extremely limited and

management of patients with CRS based solely on the low-flow theory does not lead to improved outcomes. ***(Nohria A, et al., 2008)***

A recent large trial of pulmonary artery catheter–guided management of 433 individuals admitted with acute decompensated congestive heart failure (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness [ESCAPE]) found no correlation between baseline renal function and cardiac index. ***(Nohria, et al., 2007)***.

Furthermore, improvement in cardiac index did not result in improved renal function, prevention of death, or prevention of rehospitalization. This notion is supported by the findings of multiple other investigations in which improved cardiac index or decreased pulmonary capillary wedge pressure during pulmonary artery catheter–guided therapy failed to predict improvement in renal function. ***(Weinfeld MS, et al., 1999, Mullens W, et al., 2009)*** **http://www.circ.ahajournals.org/content/121/23/2592.full - ref-17http://www.circ.ahajournals.org/content/121/23/2592.full - ref-18**

Collectively, these data do not support poor forward flow and altered hemodynamics as primary determinants of progressive renal failure in the HF population.

Intraabdominal and Central Venous Pressure Elevation

The relationship between blood pressure, cardiac output, and systemic vascular resistance is summarized by the Poiseuille law: Cardiac flow is dependent on a sufficient pressure gradient across the body's capillary networks. HF is marked by an elevation in central venous pressure, which attenuates the gradient across the glomerular capillary network. Indeed, there is increasing evidence to support roles for elevated renal venous pressure and intraabdominal pressure (IAP) in the development of progressive renal dysfunction in patients with HF.

The suggestion that elevated renal venous pressure can retard both renal blood flow and urine formation dates back to investigations performed >100 years ago.**http://www.circ.ahajournals.org/content/121/23/2592.full - ref-20** In one such early experiment, Winton observed that urine formation by isolated canine kidney was markedly reduced at renal venous pressures of 20 mm Hg and abolished at pressures >25 mm Hg. ***(Winton FR. 1931).***

Renal blood flow was also diminished in proportion to the decrease in pressure gradient across the afferent and efferent renal circulations, probably caused by the increased efferent arterial pressure. Rising renal venous pressure limited urine formation and renal blood flow more than a reduction in arterial pressure. Elevation of renal venous pressure from extrinsic compression of the veins has also been shown to compromise renal function. ***(Blake WD, et al., 1949).***

More than 60 years ago, Bradley and Bradley showed that abdominal compression to produce IAP of 20 mm Hg in normal individuals markedly reduced GFR and renal plasma flow. These relationships are supported by modern in vivo animal models. ***(Doty JM, et al., 1999)***

In recent years, there has also been increasing recognition that oliguric acute renal dysfunction frequently accompanies abdominal compartment syndrome in surgical and trauma patients. These changes are promptly reversed by abdominal decompression and may be associated with subsequent polyuria. ***(Meldrum DR, et al., 1997)***

An international panel recently defined elevated IAP as pressure ≥8 mm Hg and intraabdominal hypertension as pressure ≥12 mm Hg. In a recent study, 24 of 40 consecutive patients admitted for acute decompensated HF (mean left ventricular ejection fraction, 19%) had an IAP ≥8 mm Hg. ***(Mullens W, et al., 2008).***

None of the 40 patients in the cohort complained of abdominal symptoms at study entry. Patients with elevated IAP had significantly lower baseline GFR compared with those with normal IAP, and the degree of reduction in IAP after diuresis predicted an improvement in renal function. Other initial hemodynamic parameters such as pulmonary capillary wedge pressure and cardiac index were not different between patients with elevated IAP and those with normal IAP. The concept that venous congestion, not arterial blood flow, is an important mediator of cardiorenal failure is supported by the findings of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial, in which only baseline right atrial pressure, not arterial blood flow, correlated with baseline serum creatinine. ***(Nohria A, et al., 2008)***

The relationship between changes in IAP with diuresis and the change in serum creatinine. The close relationship suggests that increased IAP may cause renal dysfunction. Reprinted with permission from Mullens et al. ***(Nohria A, et al., 2008)***

In considering whether elevated IAP in congestive heart failure is a true culprit in the development of progressive renal dysfunction or an innocent bystander, several mechanisms by which abdominal pressure might contribute to CRS have been explored. Elevation of renal parenchymal pressure does not appear to have significant effects on GFR or renal blood flow. This was shown in studies of isolated porcine kidneys subjected to increasing amounts of extrinsic pressure. ***(Doty JM, et al., 2000)***

In contrast, elevated central and renal venous pressures offer a stronger explanation for the relationship between elevated IAP and renal dysfunction. Elevating renal venous pressure by 30 mm Hg for 2 hours in intact porcine kidneys resulted in a substantial reduction in renal blood flow and GFR. ***(Doty JM, et al., 1999)***

Furthermore, patients with HF with impaired renal function at baseline or worsening renal function during hospitalization have significantly elevated central venous pressure relative to those with less renal impairment (Figure 5). ***(Drazner MH, et al., 2001)***

In one study of intensive medical therapy directed at volume reduction, hemodynamic profiles were monitored in all patients with pulmonary artery catheters, and only elevated central venous pressure correlated with worsening versus preserved renal function. ***(Mullens W, et al., 2009)***

The role of elevated central and renal venous pressures is further supported by the association of elevated jugular venous pulsations on physical examination with higher baseline serum creatinine and increased risk for hospitalization and death caused by pump failure. ***(Drazner MH, et al., 2001)***

Finally, the association of tricuspid regurgitation with renal dysfunction was recently examined in 196 consecutive patients with HF. The authors found that patients with at least moderate tricuspid regurgitation by transthoracic echocardiography had lower estimated GFR and that a linear relationship existed between severity of tricuspid regurgitation and degree of GFR impairment. ***(Drazner MH, et al., 2001)***

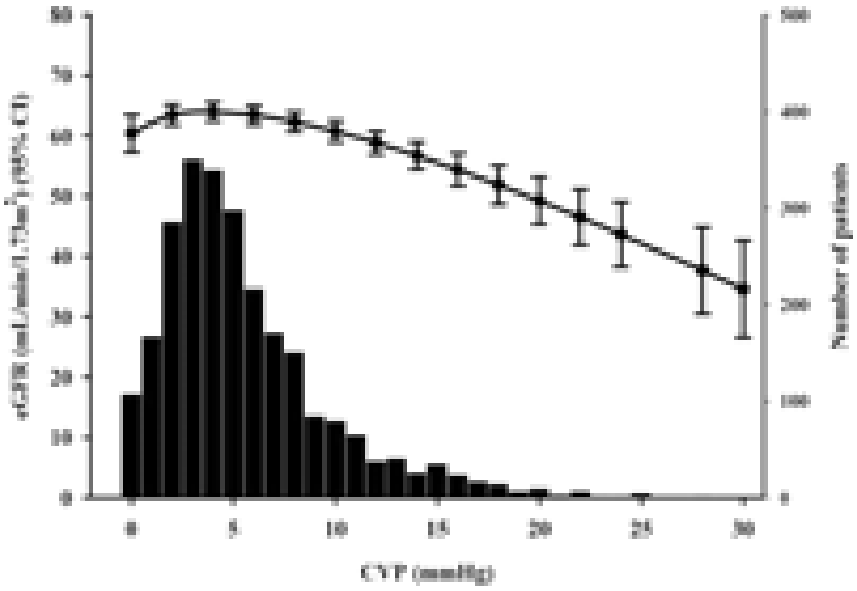


Figure 9.

Distribution of central venous pressure (CVP) and the relationship between CVP and estimated GFR in 2557 patients. CVP has repeatedly been shown to correlate well with renal dysfunction in patients with HF. Reprinted with permission from Damman et al.***(Damman K, et al., 2009)***

Sympathetic Overactivity

The adverse consequences of sympathetic nervous system activity are well known. Sustained elevated adrenergic tone causes a reduction in β-adrenergic receptor density, particularly β_1, within the ventricular myocardium, as well as uncoupling of the receptor from intracellular signaling mechanisms. Less well appreciated are the systemic effects of renal sympathetic stimulation. As left ventricular systolic failure

progresses, diminished renal blood flow and perfusion pressure (whether from arterial underfilling or renal venous congestion) lead to baroreceptor-mediated renal vasoconstriction, activation of the renal sympathetic nerves, and release of catecholaminergic hormones. This problem is compounded in patients with HF with advanced renal insufficiency because there is reduced clearance of catecholamines by the kidneys. ***(Laederach K, et al., 1987)***

There are now good data to suggest that the renal sympathetic activation leads to direct vascular effects. A recent pilot study of catheter-based renal sympathetic denervation in patients with resistant hypertension found significant improvements in GFR in 24% of patients undergoing the procedure. ***(Krum H, et al., 2009)***

Bilateral renal nerve ablation has also been shown to reduce renal norepinephrine spillover, renin activity, and systemic blood pressure 12 months later**.** ***(Schlaich MP, et al., 2009)***

Although this intervention has not been tested specifically in an HF population, denervation could possibly affect renal function and halt renal sympathetic nerve-mediated progression of cardiac failure related to elaboration of catecholamines and the RAAS. Further investigation into this exciting concept is needed to determine whether it is clinically relevant.

Renin-Angiotensin-Aldosterone Axis and Renal Dysfunction

The extreme sodium avidity and ventricular remodeling conferred by RAAS elaboration in HF are a maladaptive response to altered hemodynamics, sympathetic signaling, and progressive renal dysfunction. The benefits of angiotensin-converting enzyme (ACE) inhibition and aldosterone antagonism through blockade of the intracardiac RAAS, reduction in adrenergic tone, improvement in endothelial function, and

prevention of myocardial fibrosis are well described in cardiac failure; RAAS inhibition has been a main focus of therapy in HF for the last 2 decades and has led to improved outcomes for many patients. Unfortunately, little is known about the long-term benefits or adverse effects of RAAS inhibition on kidney function in HF.

ACE inhibitors and angiotensin receptor blockers have important renoprotective effects in hypertensive patients with nondiabetic renal disease and individuals with diabetic nephropathy. ***(Lewis EJ, et al., 1993)***

In contrast, whether there is a renoprotective role of ACE inhibitors and angiotensin receptor blockers in systolic HF that is independent of direct preservation of ventricular function has not been established. ACE inhibitors and angiotensin receptor blockers cause dose-dependent increases in angiotensin II (AT-II). ***(Gottlieb SS, et al., 1993)***

This may contribute to the phenomenon described as escape from ACE inhibition. Significantly, AT-II directly contributes to kidney damage. AT-II upregulates the cytokines transforming growth factor-β, tumor necrosis factor-α, nuclear factor-κB, and interleukin-6 and stimulates fibroblasts, resulting in cell growth, inflammation, and fibrotic damage in the renal parenchyma. ***(Ruiz-Ortega M, et al., 2002)***

Oxidative Injury and Endothelial Dysfunction

Neurohormones are strong precipitants and mediators of an oxidative injury cascade that leads to widespread endothelial dysfunction, inflammation, and cell death in the CRS. AT-II seems to be particularly important in this process, exerting many deleterious effects through the activation of NADPH oxidase and NADH oxidase. AT-II activates these 2 enzymes within vascular smooth muscle cells, cardiac myocytes, and renal tubular epithelial cells, generating superoxide, a reactive oxygen species. ***(Vaziri ND, et al., 2003)***

Reactive oxygen species have many unfavorable effects in living tissues and likely contribute to the processes of aging, inflammation, and progressive organ dysfunction. Growing evidence supports oxidative injury as a common link between progressive cardiac and renal dysfunction. Because both primary cardiac failure and primary renal failure lead to elaboration of the RAAS, activation of oxidases by AT-II in one organ has the potential to lead to progressive dysfunction in the secondary organ through reactive oxygen species generation.

Inactivation of nitric oxide is a particularly important effect of superoxide and other reactive oxygen species. Decreased bioavailability of nitric oxide may partially explain the endothelial dysfunction observed in vascular smooth muscle and abnormal contractile properties of cardiac myocytes in HF. There is heightened NADPH oxidase activity in explanted failing hearts compared with healthy hearts awaiting implantation, and high-dose antioxidant agents attenuate left ventricular remodeling after experimental ligation of the left anterior descending coronary artery. ***(Kinugawa S, et al., 2000)***

Dahl salt-sensitive rats with systolic HF have substantial elevations in AT-II and NADPH oxidase expression and reduced nitric oxide production in kidney tissue compared with control animals without experimental HF. ***(Tojo A, et al., 2002)***

Interestingly, these changes were prevented with the ACE inhibitor imidapril. Other groups have shown that both ACE inhibitors and angiotensin receptor blockers increased the availability of nitric oxide through upregulation of superoxide dismutase. ***(Hornig B, et al., 2001)***

These observations provide a good example of dysfunction in a secondary organ, in this case kidney, associated with primary disease in another organ.

Erythropoietin and the Cardiorenal-Anemia Syndrome

Anemia is common in individuals with chronic kidney disease and HF and may contribute to the abnormal renal oxidative state; hemoglobin is an antioxidant. Although anemia should induce increased erythropoietin, there is evidence that decreased concentrations in patients with CRS may directly exacerbate the renal abnormalities. Therefore, the combination of anemia and decreased erythropoietin may exacerbate the underlying factors causing CRS.

The high frequency of anemia in CRS and HF has repeatedly been demonstrated. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry, 51% of the nearly 50 000 patients with HF had hemoglobin ≤12 g/dL and 25% had hemoglobin between 5 and 10.7 g/dL. ***(Young JB, et al., 2008)***

Patients with HF with anemia had increased mortality, length of hospital stay, and hospital readmission rates compared with nonanemic patients with HF. It should be noted that anemia in advanced kidney diseases is due to an absolute deficiency in erythropoietin production. HF alone, on the other hand, may be marked by insensitivity to elevated erythropoietin concentrations secondary to sustained inflammation. Patients with both HF and kidney disease, however, may have low erythropoietin concentrations. ***(George J, et al., 2005)***

The lack of erythropoietin could exacerbate HF in multiple ways. In cardiac cells, erythropoietin can prevent apoptosis and increase the number of cardiomyocytes. ***(Calvillo L, et al., 2003)***

Similar observations have been made in renal cells. Although it is unclear what effect erythropoietin has on nitric oxide synthesis, it does appear to decrease oxidative stress. ***(Jie KE, et al., 2006)***

Small studies suggest that these actions might exert clinical benefit. In a single-center prospective trial, 32 anemic NYHA class II to IV patients were randomized to receive erythropoietin and intravenous iron or routine management. After a mean follow-up of 8 months, patients with active treatment demonstrated improved ejection fraction by multigated acquisition, decreased diuretic requirements, unchanged serum creatinine, and improvements in NYHA functional class. Control patients had worsened ejection fraction, worsening serum creatinine, and deterioration in NYHA functional class. ***(Silverberg DS, et al., 2000)***

Unfortunately, this study was not placebo controlled or blinded. Other studies have focused on clinical benefits and have not carefully evaluated possible mechanisms.

At this point, it is therefore unclear whether anemia is a marker of progressive heart and renal failure or a true mediator of the CRS. Further long-term study is needed to address the interesting possibility that treatment of anemia in HF may improve renal function. Studies of patients with advanced renal disease suggest that partial correction of anemia leads to improved quality of life, reduced progression to end-stage renal disease, and reduced mortality. ***(Mohanram A, et al., 2004)***

Because aggressive correction of anemia in this population has been associated with high rates of adverse events, exploring the utility of correcting anemia in patients with HF should be done with caution. ***(Singh AK, et al., 2006)***

Other Renal Targets

Arginine vasopressin is a nonapeptide that is released by oncotic stimuli but also by blood pressure and cardiac factors. Concentrations are increased in HF and could lead to water retention and hyponatremia. ***(Goldsmith SR, et al., 1983)***

Furthermore, it has vasoactive effects (mainly through V_1 receptors) that could be important. More clearly relevant to patients with HF is that activation of the V_2 receptor increases the permeability to water of the renal collecting tubular cells, resulting in water retention. Vasopressin antagonists have been shown to lead to more aquaresis and resolution of hyponatremia, with some weight loss and improvement in overall fluid balance. However, these effects have not resulted in clear demonstrable clinical benefit or improvement in renal function. ***(Konstam MA, et al., 2007)***

At present, vasopressin appears important as a cause of water retention in some patients but does not appear integral to renal function in these patients.

The importance of adenosine as a mediator of the CRS is also not known. Adenosine-A_1 receptors are found in afferent arterioles, juxtaglomerular cells, the proximal tubule, and thin limbs of Henle, and GFR and urine output could improve by countering the effects of adenosine. Indeed, adenosine concentrations are increased in patients with HF. ***(Funaya H, et al., 1997)***

Initial studies suggested that this mechanism was important. An adenosine-A_1 antagonist, BG9719, maintained creatinine clearance while permitting diuresis. In a crossover study of another adenosine-A_1 antagonist, rolofylline, GFR increased by 32% with active drug, and renal plasma flow increased by 48%. ***(Gottlieb SS, et al., 2002)***

Unfortunately, the pivotal Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT), recently presented at the European Society of Cardiology (2009), showed no beneficial effects in patients with acute decompensated HF. The reason for the very different results between the early studies and PROTECT is unknown. It could reflect the lack of

importance of adenosine as a mediator of the CRS or could indicate problems with the drug or the particular patient population studied.

Shown below is an image summarizing the bidirectional relationship between the heart and the kidneys in the pathophysiology of the cardiorenal syndrome.

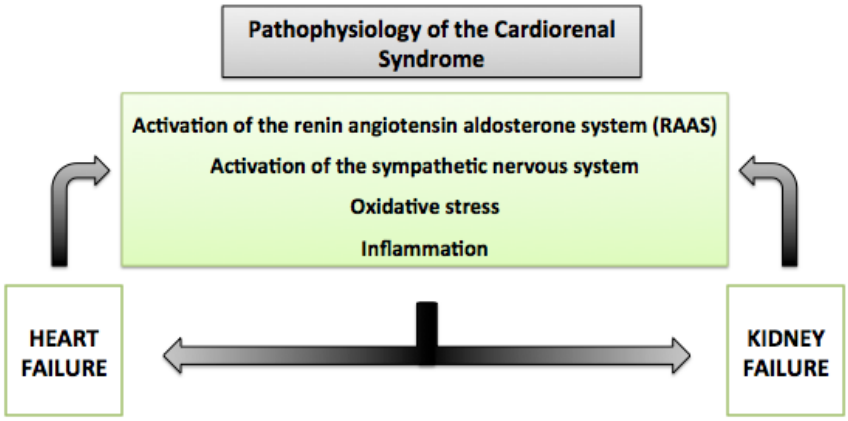


Figure 7

Shown below is an image showing the complex pathophysiological mechanisms involved in the cardiorenal syndrome.

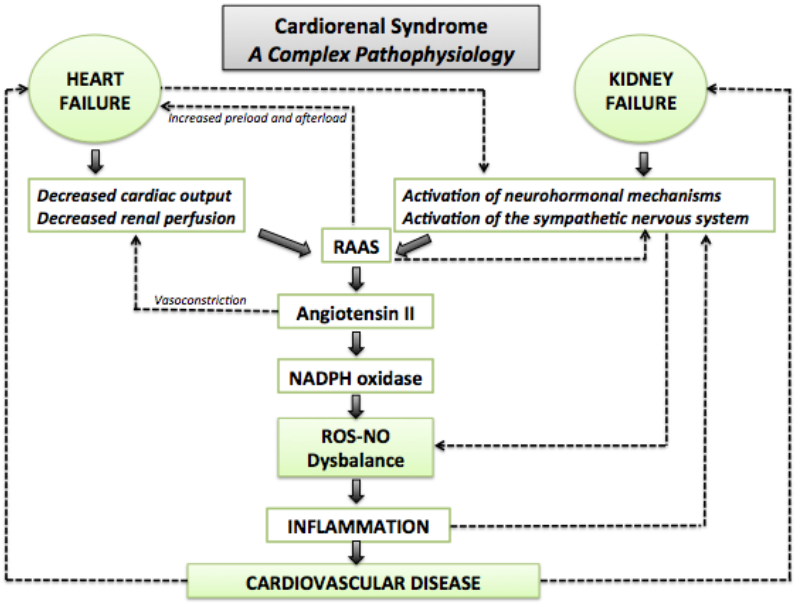


Figure 8

Biomarkers of Cardiorenal Syndromes

- Despite the efficient use of cardiac biomarkers that detect early injury, the detection of acute kidney injury before the consequential fall of GFR has not been possible with the current utilization of serum creatinine. It has become therefore imperative to search for new biomarkers that can readily identify renal damage and thus cardiorenal syndromes rapidly for prompt and efficient management.
- Several novel biomarkers have been introduced to the literature. Nonetheless, none has yet effectively replaced the use of serum creatinine in clinical settings.

Catalytic Iron

- Catalytic iron is based on the use of bleomycin detectable assay to detect catalytic iron in CRS at the level of generation of reactive oxygen species.
- It is a potential diagnostic and therapeutic target for CRS ***(Lele, S., et al., 2009)***.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) or Siderocalin

- It scavenges cellular and pericellular labile iron.
- It has been studied extensively in animal and human models; it increases significantly in plasma and urine ***(Mori, K., et al., 2007)***.

Cystatin C

- It is a cysteine protease inhibitor.
- At the level of the kidney, it is freely filtered, and completely reabsorbed.
- Cystatin C is better than creatinine in estimating GFR and chronic kidney disease status ***(McMurray, M., et al., 2009).***

Other Biomarkers

- Other previous and emerging biomarkers for CRS include Kidney Injury Molecule 1 (KIM-1) ***(Kobayashi, M., et al., 2010)***, N-Acetyl-B-(D) Glucosaminidase (NAG) ***(Wellwood, J., et al., 1975)***, Interleukin-18 (IL-18) ***(Parikh, C., et al., 2005)***, Liver Fatty Acid-Binding Protein (L-FABP) ***(Noiri, E., et al., 2009)***, and Tubular Enzymuria such as gamma glutamyl transpeptidase (GGT), alkaline phosphatase, lactate dehydrogenase, and α and π glutathione S-transferase (GST) ***(Liang, X., et al., 2010, and Endre, Z., 2008).***

Patient and methods

This study was conducted on two hundred and fifty patients with cardio-renal syndrome in Banha University hospitals in nine months duration.

Age of those patients ranged from 20-65 years with mean age 41.56 ± 4.49 of those 145 were male and 105 female.

The patients were recruited from those patients admitted in Internal medicine, Cardiology, ICU, Chest, Rheumatology, Cardiothoracic surgery departments of Benha University hospitals. Diagnosis of acute decompensated heart failure and chronic heart failure was made according to clinical manifestations and echocardiography. Diagnosis of acute kidney injury according to RIFLE criteria.

	GFR criteria	Urine output criteria
Risk	1·5-fold increase in S_{creat} or GFR decrease >25%	UO <0·5 mL/kg/h for 6 h
Injury	Two-fold increase in S_{creat} or GFR decrease >50%	UO <0·5 mL/kg/h for 12 h
Failure	Three-fold increase in S_{creat}, GFR decrease >75%, S_{creat} ≥4 mg/dL, or acute rise in S_{creat} ≥0·5 mg/dL	UO <0·3 mL/kg/h for 24 h or anuria for 12 h
Loss	Complete loss of kidney function >4 weeks	
ESKD	End-stage kidney disease (>3 months)	

Figure 1: **RIFLE criteria for acute kidney injury**
Adapted from Bellomo and colleagues.[1] As GFR or UO deteriorate, the patient moves from risk (class R) to failure (class F). Class R has a high sensitivity and class F a high specificity for acute kidney injury. RIFLE=risk, injury, failure, loss, end stage. GFR=glomerular filtration rate. S_{creat}=serum creatinine concentration. UO=urine output. ESKD=end-stage kidney disease.

Diagnosis of chronic kidney disease was made according to estimated glomerulis filtration rate using CKD-EPI formula.

Inclusion criteria:-

1- Patients with acute decompensated heart failure and acute kidney injury secondary to heart failure.

2- Patients with chronic heart failure with chronic kidney disease secondary to heart failure.

3- Patients with chronic kidney disease with cardiac dysfunction secondary to CKD.

4- Patients with acute kidney injury with cardiac dysfunction secondary to AKI.

5- Patients with systemic disease affecting both cardiac and renal functions.

Exclusion criteria:-

1- Age below 20 years.

2- Patients with CKD without cardiac dysfunction.

3- Patients with AKI without cardiac dysfunction.

4- Patients with heart failure without renal impairment.

5- Patients with cardio renal impairment without pathophysiologic relation to each other (eig polycystic kidney disease and ischaemic heart disease).

All patients were subjected to thorough history taking and clinical examination with stress on the following:-

1- Manifestations of right or left sided heart failure or both.

2- Urine out put.

3- Uraemic manifestations (persistent vomiting, itching, ….)

The following investigations were done to all subjects:-

- Serum creatinine and blood urea.
- Urine analysis.
- Estimated glomerular filtration rate using CKD-EPI equations.
- CBC.
- Serum Na^+ and serum K^+
- Arterial blood gases.
- Fasting and 2 hour post prandial plasma glucose.
- Lipid profile including LDL-C, HDLC, VLDL-C and triglycerides.
- ESR and CRP.
- ALT and AST.
- Pelvi-abdominal ultrasound.
- Echo. cardiography.
- ECG.

Estimated GFR (eGFR) using the CKD-EPI formula:

The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula was published in May 2009. It was developed in an effort to create a formula more accurate than the MDRD formula, especially when actual GFR is greater than 60 mL/min per 1.73 m2.

Researchers pooled data from multiple studies to develop and validate this new equation. They used 10 studies that included 8254

participants, randomly using 2/3 of the data sets for development and the other 1/3 for internal validation. Sixteen additional studies, which included 3896 participants, were used for external validation.

The CKD-EPI equation performed better than the MDRD (Modification of Diet in Renal Disease Study) equation, especially at higher GFR, with less bias and greater accuracy. When looking at NHANES (National Health and Nutrition Examination Survey) data, the median estimated GFR was 94.5 mL/min per 1.73 m2 vs. 85.0 mL/min per 1.73 m2, and the prevalence of chronic kidney disease was 11.5% versus 13.1%.

The CKD-EPI equation, expressed as a single equation, is:

$$\mathrm{eGFR} = 141 \times \min(\mathrm{SCr/k},1)^{a} \times \max(\mathrm{SCr/k},1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ Female] \times [1.159\ if\ Black]$$

Where SCr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is - 0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

A clearer version may be as follows: For creatinine (IDMS calibrated) in mg/dL:

Black Female

If serum creatinine (Scr) <= 0.7

$$\mathrm{eGFR} = 166 \times (\mathrm{SCr}/0.7)^{-0.329} \times 0.993^{Age}$$

If serum creatinine (Scr) > 0.7

$$\mathrm{eGFR} = 166 \times (\mathrm{SCr}/0.7)^{-1.209} \times 0.993^{Age}$$

Black Male

If serum creatinine (Scr) <= 0.9

$$\mathrm{eGFR} = 163 \times (\mathrm{SCr}/0.9)^{-0.411} \times 0.993^{Age}$$

If serum creatinine (Scr) > 0.9

$$\mathrm{eGFR} = 163 \times (\mathrm{SCr}/0.9)^{-1.209} \times 0.993^{Age}$$

White or other race Female

If serum creatinine (Scr) <= 0.7

$$\mathrm{eGFR} = 144 \times (\mathrm{SCr}/0.7)^{-0.329} \times 0.993^{Age}$$

If serum creatinine (Scr) > 0.7

$$\mathrm{eGFR} = 144 \times (\mathrm{SCr}/0.7)^{-1.209} \times 0.993^{Age}$$

White or other race Male

If serum creatinine (Scr) <= 0.9

$$\mathrm{eGFR} = 141 \times (\mathrm{SCr}/0.9)^{-0.411} \times 0.993^{Age}$$

If serum creatinine (Scr) > 0.9

$$\mathrm{eGFR} = 141 \times (\mathrm{SCr}/0.9)^{-1.209} \times 0.993^{Age}$$

This formula was developed by Levey et al *(, 2009e).*

The formula CKD-EPI may provide improved cardiovascular risk prediction over the MDRD Study formula in a middle-age population ***(Matsushita et al., 2010a).***

Data management

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 16 to obtain:

Descriptive data

Descriptive statistics were calculated for the data in the form of:

1. Mean and standard deviation for quantitative data.
2. Frequency and distribution for qualitative data.

Analytical statistics

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:-

1- ANOVA test (F value):-Used to compare mean of more than two groups of quantitative data**.**

2- Inter-group comparison of categorical data was performed by using chi square test **(X^2-value)** and fisher exact test (FET).

A *P* value <0.05 was considered statistically significant (S) while >0.05 statistically insignificant P value <0.01 was considered highly significant (HS) in all analyses.

Results:

Table 1: Shows the age and sex distribution of the study group.

		No (250)	%
Age	Mean ±SD (range)	41.56 ±4.49 (20-65)	
Sex no &%	Male	145	58.0
	Female	105	42.0

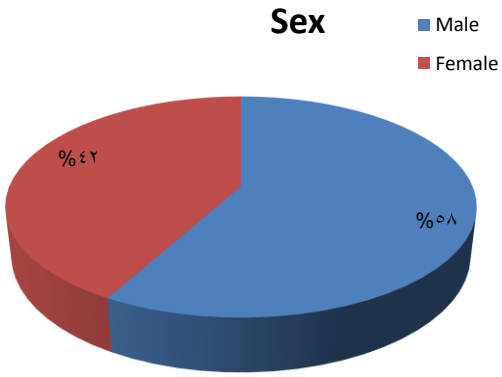


Table 2: Shows the prevalence of different types of cardiorenal syndrome.

Types of CRS	I	27	10.8
	II	76	30.4
	III	13	5.2
	IV	51	20.4
	V	83	33.2

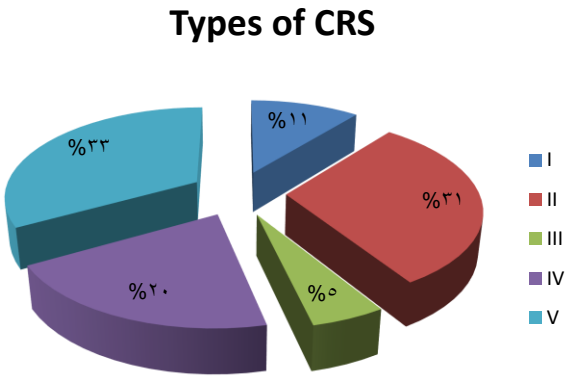
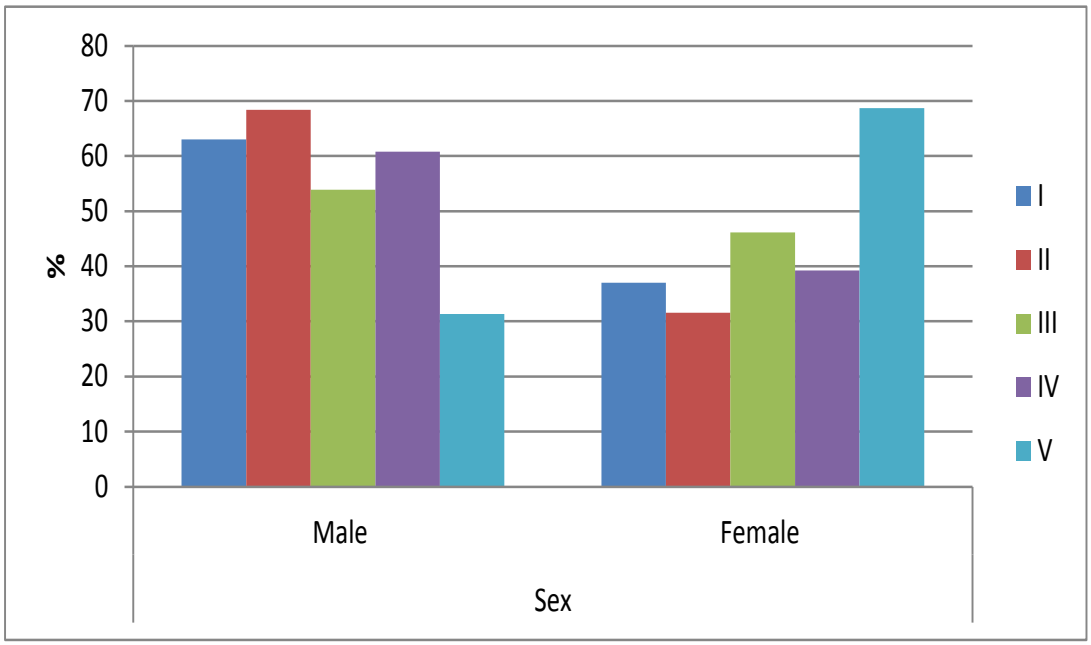


Table3: Shows the age and sex distribution of different types of cardiorenal syndrome.

Types of CRS		I		II		III		IV		V		test	P value
		No	%	No	%	No	%	No	%	No	%		
Sex	Male	17	63.0	52	68.4	7	53.9	31	60.8	26	31.3	25.24	0.001
	Female	10	37.0	24	31.6	6	46.1	20	39.2	57	68.7		
Age	Mean±SD	42.22±4.26		41.53±3.93		41.54±4.25		41.31±4.06		41.53±5.33		0.185	0.946



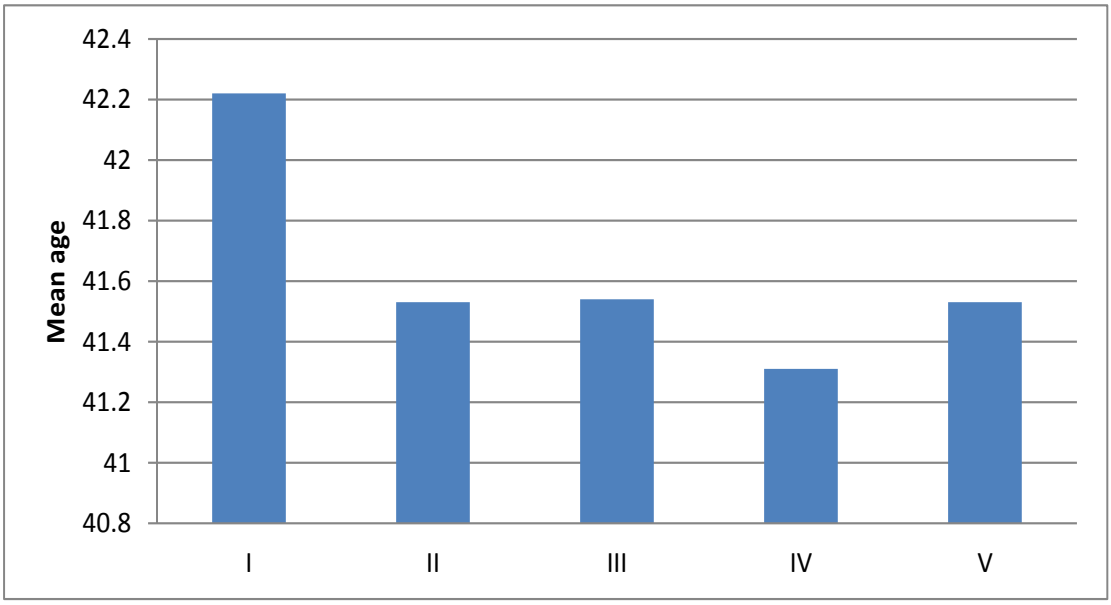


Table 4: Shows the prevalence of cardiorenal syndrome in different departments in Benha University Hospitals.

	Types of CRS	I		II		III		IV		V		test	P value
		No	%	No	%	No	%	No	%	No	%		
Department	Internal medicine	2	7.4	42	55.3	5	38.5	43	84.3	45	54.2	96.16	0.001
	Cardiology	14	51.9	25	32.9	2	15.4	2	3.9	16	19.3		
	ICU	6	22.2	3	4.0	6	46.2	5	9.8	10	12.1		
	Chest	2	7.4	4	5.3	0	0.0	0	0.0	2	2.4		
	Rheumatology	0	0.0	0	0.0	0	0.0	0	0.0	10	12.1		
	Cardiothoracic surgery	3	11.1	2	2.6	0	0.0	1	2.0	0	0.0		

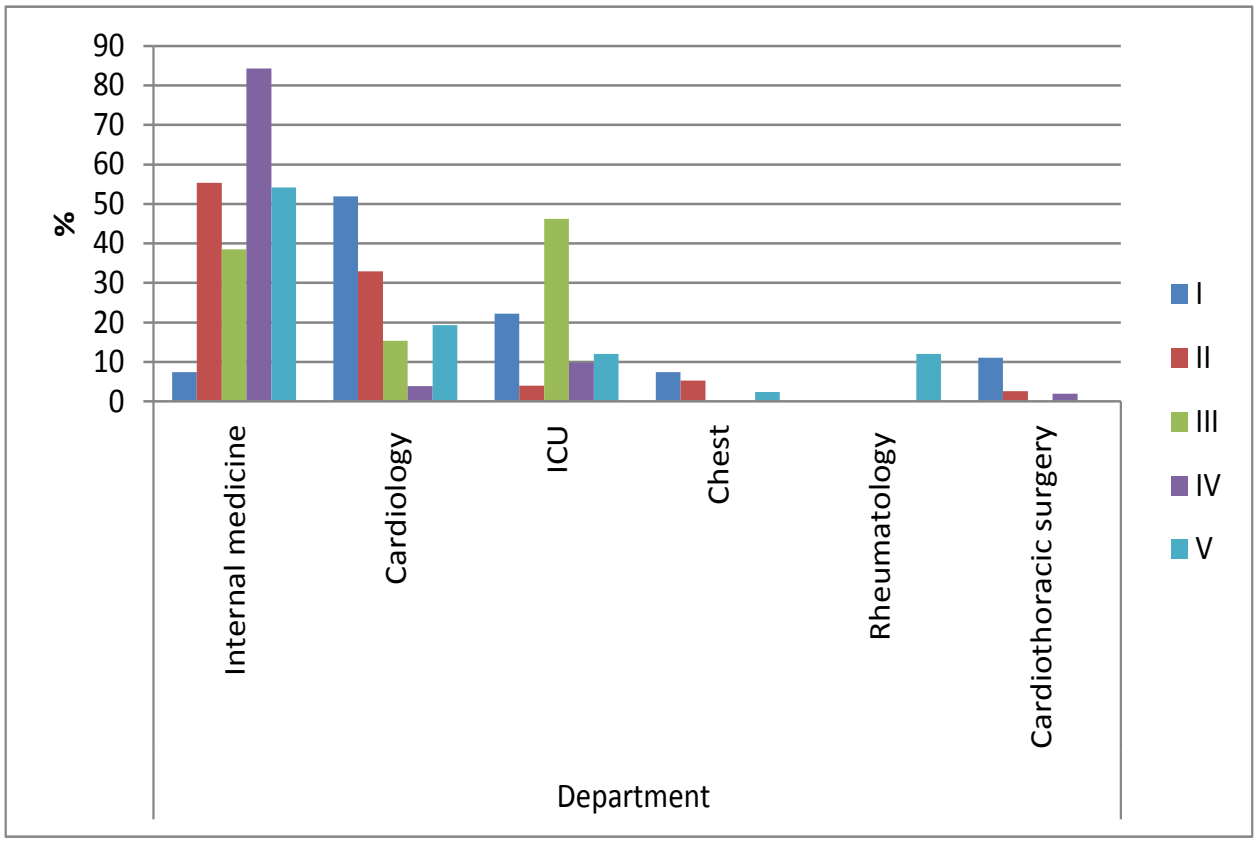


Table 5: Shows the mortality rate of cardiorenal syndrome in Benha University Hospitals.

	Types of CRS	I		II		III		IV		V		test	P value
		No	%	No	%	No	%	No	%	No	%		
Mortality	Died	3	11.1	0	0.0	0	0.0	0	0.0	4	4.8	12.13	0.016
	Survived	24	88.9	76	100	13	100	51	100	79	95.2		

Table 6: Shows the effect of cardiorenal syndrome on Hospital stay.

	Types of CRS	I		II		III		IV		V		test	P value
		No	%	No	%	No	%	No	%	No	%		
Hospital stay	Increased	3	11.1	36	47.4	7	53.9	31	60.8	53	63.9	25.01	0.001
	Not changed	24	88.9	40	52.6	6	46.1	20	39.2	30	36.1		

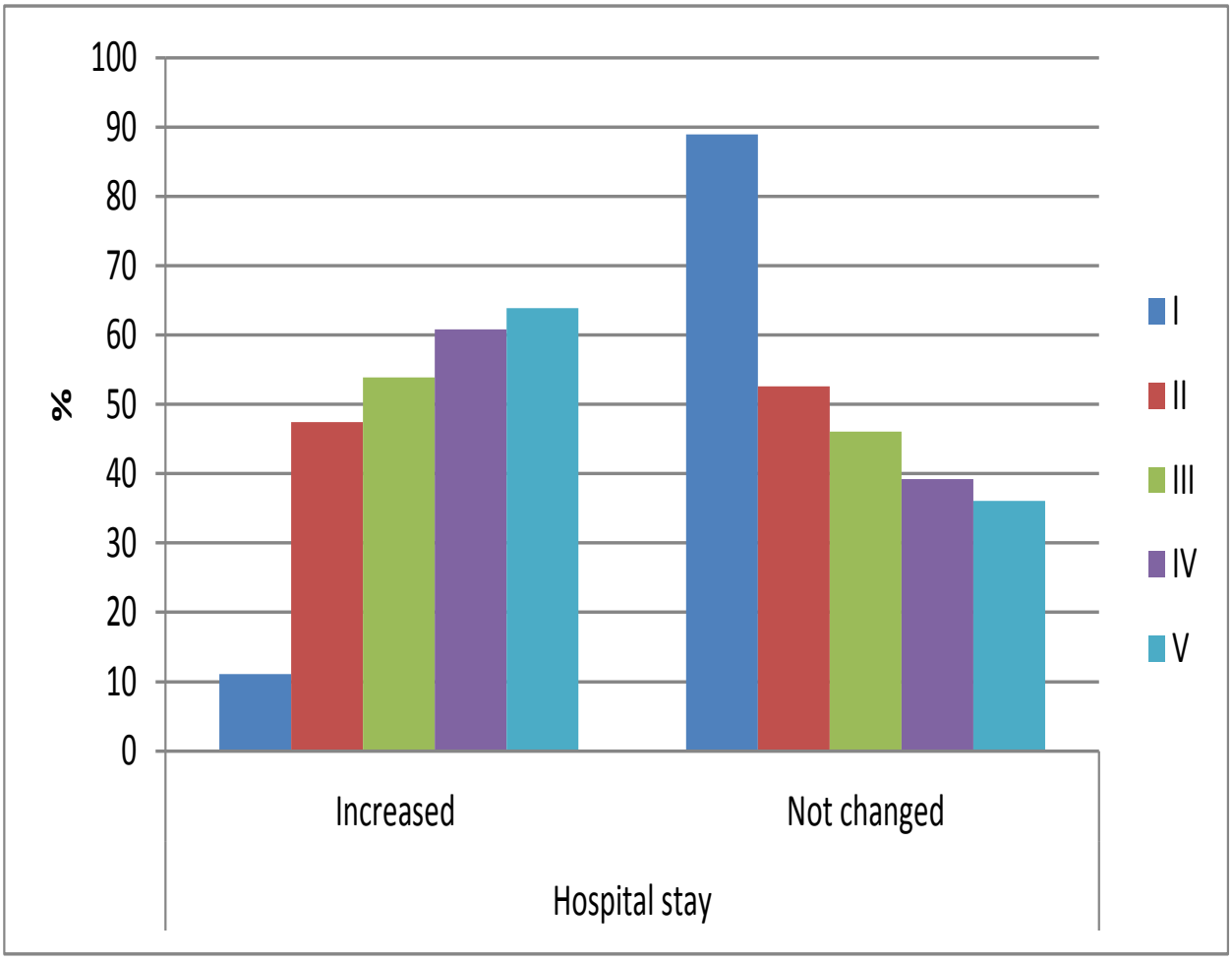
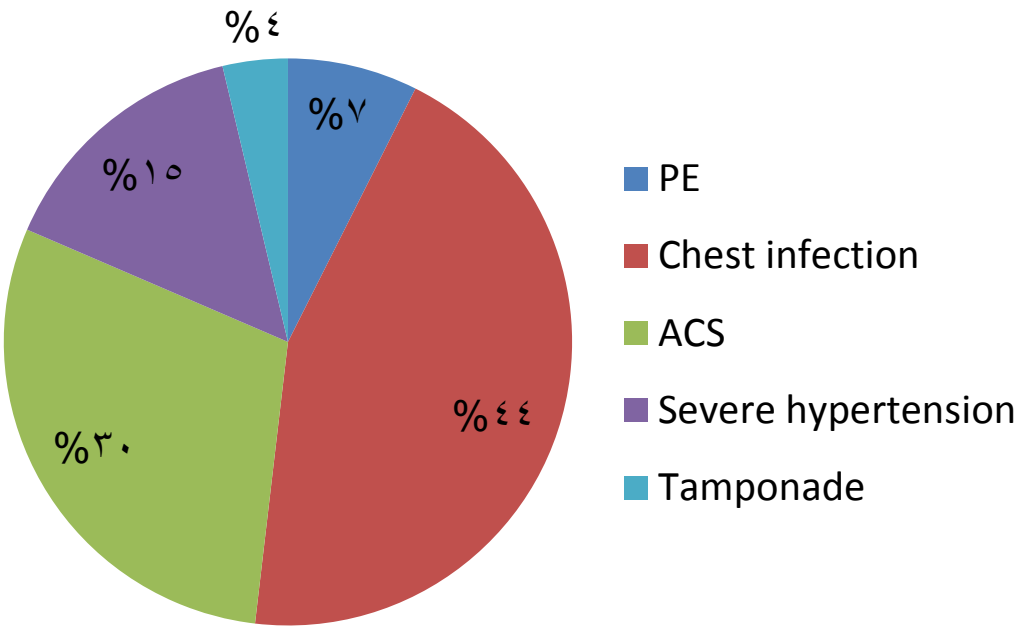


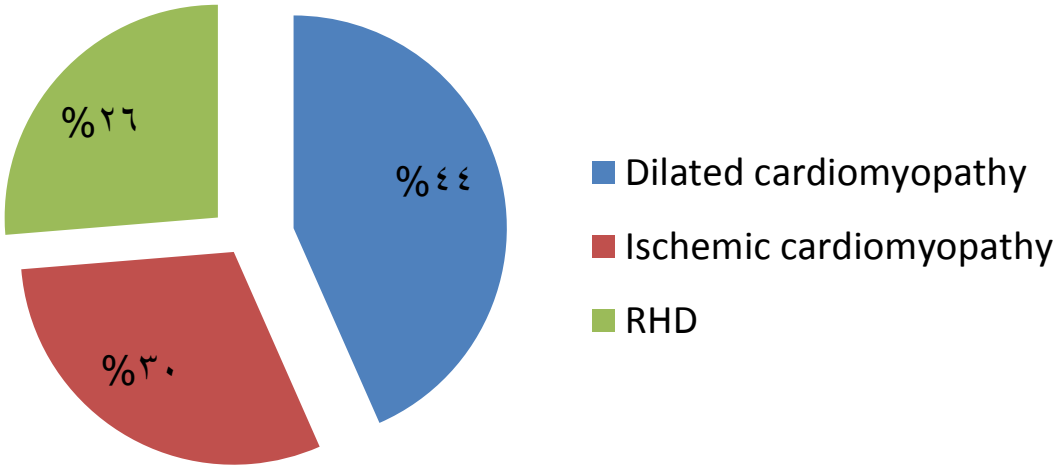
Table 7: Shows the most common causes of cardiorenal syndrome in Benha University Hospitals.

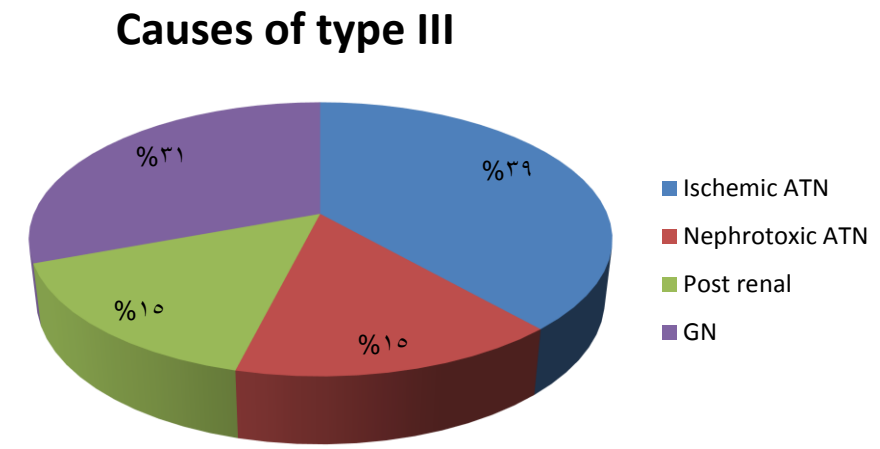
Causes of different types of CRS		No	%
Type I (27)	PE	2	7.4
	Chest infection	12	44.4
	ACS	8	29.6
	Severe hypertension	4	14.8
	Tamponade	1	3.7
Type II (76)	Dilated cardiomyopathy	33	43.4
	Ischemic cardiomyopathy	23	30.3
	RHD	20	26.3
Type III(13)	Ischemic ATN	5	38.5
	Nephrotoxic ATN	2	15.4
	Post renal	2	15.4
	GN	4	30.7
Type IV(51)	ESRD	21	41.2
	Chronic GN	14	27.5
	Analgesic nephropathy	12	23.5
	Chronic interstitial nephritis	2	3.9
	APKD	2	3.9
Type V(83)	Lupus	5	6.0
	Sepsis	3	3.6
	DM	43	51.8
	HTN	32	38.6

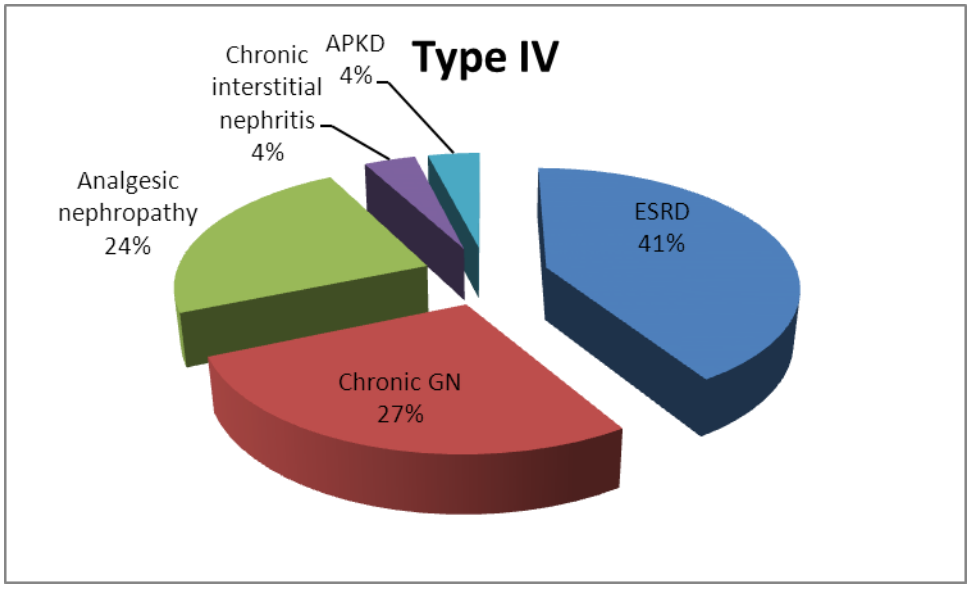
Causes of type I



Causes of typeII




Causes of type III
%٣١
%٣٩
%١٥
%١٥
Ischemic ATN
Nephrotoxic ATN
Post renal
GN


Type IV
Chronic interstitial nephritis 4%
APKD 4%
Analgesic nephropathy 24%
ESRD 41%
Chronic GN 27%

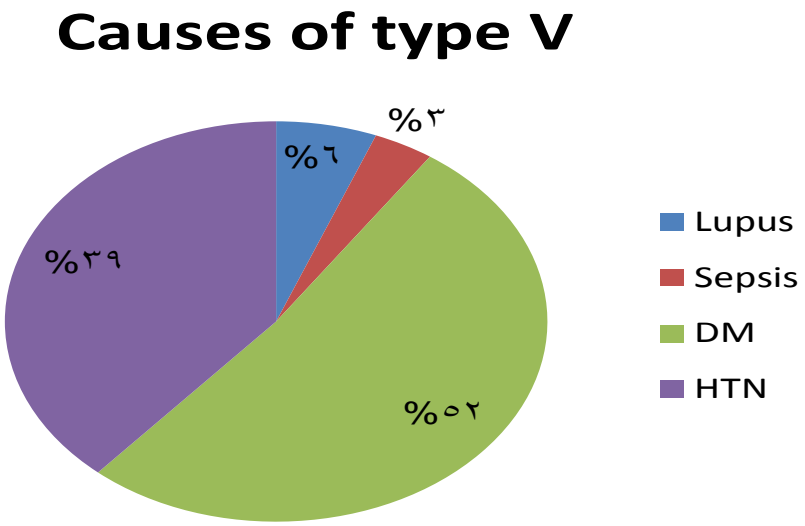
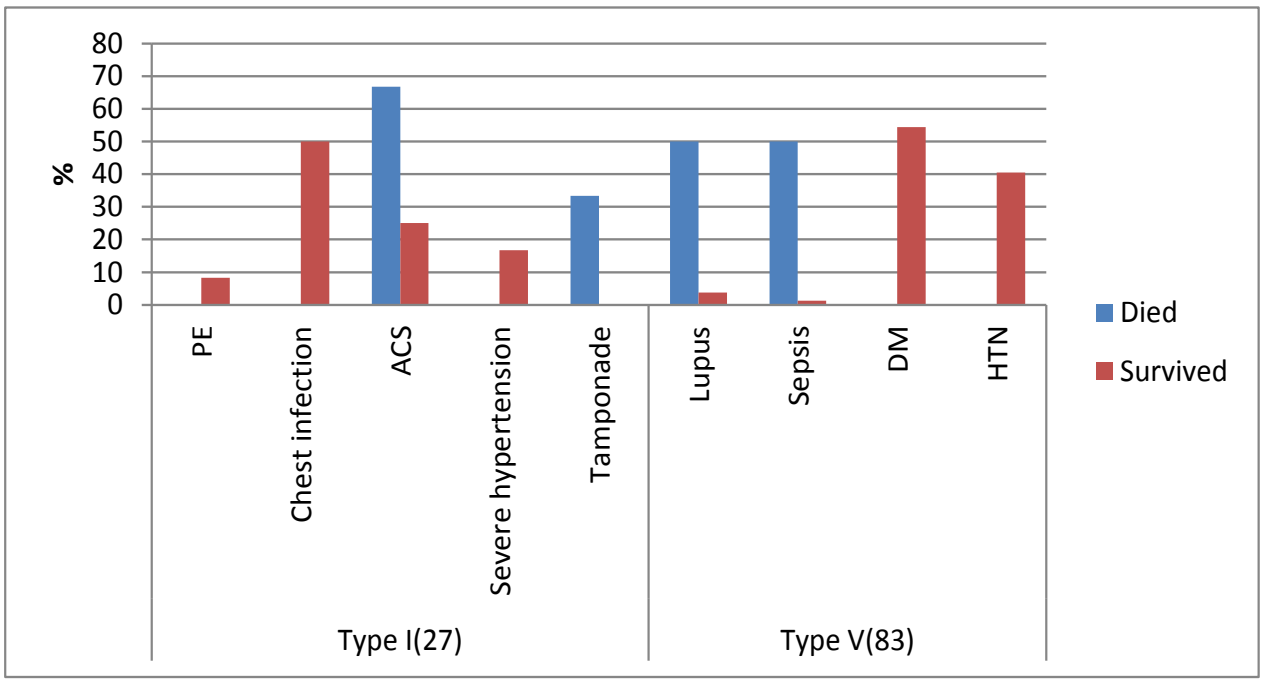

Causes of type V
%٣
%٦
%٣٩
%٥٢
Lupus
Sepsis
DM
HTN

Table 8: Shows the mortality rate of cardiorenal syndrome in type 1 and type 5 cardiorenal syndrome.

Causes of different types of CRS \ Mortality		Died		Survived		Total		test	P value
Type I(27)	PE	0	0.0	2	8.3	2	7.4	11.81	0.019
	Chest infection	0	0.0	12	50.0	12	44.4		
	ACS	2	66.7	6	25.0	8	29.6		
	Severe hypertension	0	0.0	4	16.7	4	14.8		
	Tamponade	1	33.3	0	0.0	1	3.7		
Type V(83)	Lupus	2	50.0	3	3.8	5	6.0	42.31	0.001
	Sepsis	2	50.0	1	1.3	3	3.6		
	DM	0	0.0	43	54.4	43	51.8		
	HTN	0	0.0	32	40.5	32	38.6		



Discussion

There is no epidemiological data regarding prevalence and incidence of CRS in a medical ward. Some observational studies evaluated the development of AKI in association with acute decompensated heart failure and acute coronary syndrome. These studies were performed retrospectively therefore they present some limitations ***(Bagshaw SM, et al., 2010)*.**

Cardiorenal syndrome is a condition which is more frequently observed in the clinical practice as renal insufficiency occurs in at least one third of patients with acute and chronic heart failure and conversely most of patients suffering from renal failure develop heart disease ***(Mullens w , et al., 2009) .***

In both acute and chronic pathological conditions, a careful evaluation of possible interactions between heart and kidney dysfunction is important because of practical implications, not only for early diagnosis, but also for optimization of management. Unfavourable effects of volume overload and venous congestion are well known in the course of CRS ***(Cushman et al., 2010)*.**

Correction of volume overload in the setting of heart failure is complicated as the use of diuretic therapy was the mainstay in reducing volume overload, unfortunately diuretic resistance is common particularly in advanced stages of CRS ***(Turner et al., 2012).***

In the Acute Decompensated Heart Failure National Registry (ADHERE) of >105 000 individuals admitted for acute decompensated

HF, 30% had a history of renal insufficiency, 21% had serum creatinine concentrations >2.0 mg/dL, and 9% had creatinine concentrations >3.0 mg/dL. McAlister et al found that only 17% of 754 outpatients with HF had creatinine clearances >90 mL/min. 39% with New York Heart Association (NYHA) class IV symptoms and 31% with NYHA class III symptoms had creatinine clearance <30 mL/min. These numbers are striking when one considers the complexity of treating volume overload in those with coexistent renal disease and that there are >1 million hospital admissions for decompensated HF in the United States annually. ***(McAlister FA, et al., 2003).***

Renal dysfunction is one of the most important independent risk factors for poor outcomes and all-cause mortality in patients with HF. Baseline glomerular filtration rate (GFR) appears to be a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class. Both elevated serum creatinine on admission and worsening creatinine during hospitalization predict prolonged hospitalization, rehospitalization, and death. ***(Hillege HL, et al., 2000).***

On the basis of estimates provided by the Third National Health and Nutrition Examination Survey (NHANES III), almost 8 million individuals living in the United States have a GFR <60 mL/min. ***(Coresh J, et al., 2003).***

Patients with chronic renal insufficiency are at strikingly higher risk for myocardial infarction, HF with systolic dysfunction, HF with preserved left ventricular ejection fraction, and death resulting from cardiac causes compared with individuals with normal GFR**.** ***(Foley RN, et al., 1998).***

A recent meta-analysis suggests that individuals with primary renal disease are more likely to eventually die of cardiovascular causes than renal failure itself. ***(Tonelli M, et al., 2006)*.**

This is not just secondary to atherosclerotic disease; in a multicenter cohort study of 432 patients, 31% planning to initiate hemodialysis had HF symptoms, and 33% of such patients had estimated left ventricular ejection fraction <40% ***(Harnett JD, et al., 1995).***

Patients with HF and new hemodialysis had a median survival of only 36 months compared with 62 months in patients without HF. Furthermore, 25% who did not have HF symptoms on initiation of dialysis developed these symptoms after a median follow-up of 15 months. Conversely, reversal of renal dysfunction can improve cardiac function. In a study of 103 hemodialysis patients with HF and left ventricular ejection fraction <40%, the mean ejection fraction increased from 32% to 52% after renal transplantation, and 70% had normalization of cardiac function. ***(Wali RK, et al., 2005).***

Hypertensive heart disease and HF with a normal ejection fraction are common among individuals with advanced and end-stage renal disease. One study showed that there is echocardiographic evidence of left ventricular hypertrophy in 45% of individuals with creatinine clearance <24 mL/min and in 70% of those planning to initiate hemodialysis**. *(Levin A, et al., 1996)*.**

Renal disease patients with left ventricular hypertrophy have accelerated rates of coronary events and markers of uremia compared with

those with normal left ventricular mass, and a high proportion of these individuals develop clinical HF**. *(Parfrey PS, et al., 1996).***

. In our study in Benha university hospitals 250 patients were divided into five types of CRS : 27 patients had clinical signs compatible with a diagnosis of CRS type 1(10.8%), 76 patients had CRS type 2(30.4%) , 13 patients had CRS type 3 (5.2%) , 51 patients had CRS type 4 (20.4%) and 83 patients had CRS type 5 (33.2%).

In a study on the prevalence of cardiorenal syndrome conducted by Gigante, et al in the department of clinical medicine in Sapienza university of Rome, Rome, Italy where 190 patients were divided into five types of CRS: 61 patients had clinical signs compatible with a diagnosis of CRS type 1(32.1%), 30 patients had CRS type 2(15.8%), 15 patients had CRS type 3(7.9%), 11 patients had CRS type 4(4.8%) and 73 patients had CRS type 5(38.4%) ***(Gigante et al., 2014).***

In our study CRS were more common in males , the mean age of the study group was 41.56 **±** 4.49 years.

Gigante study settled that CRS were more common in males (68.9%) of patients; the mean age of the study group was 77.7±4.8 years ***(Gigante, et al.,2014).***

In our study, CRS type 1 and 5 were the two classes with highest rate of mortality where 3 patients of 27 studied patients with type 1 CRS died (11.1%) and 4 patients of 83 patients studied with type 5 CRS died (4.8%) *(P value 0.016).*

The cause of death in type 1 CRS was attributed to acute coronary syndrome in 2 patients with cardiogenic shock and AKI and 1 patient died from cardiac tamponade ***(P value 0.019).***

Gigante, et al study documented that CRS type 1 is the class of highest rate of morbidity and mortality possibly due to the severity of heart failure as well as the higher age at presentation, CRS type 5 was the second class regarding mortality probably due to many clinical situations in which both organs are targeted simultaneously by systemic illness such as sepsis, vasculitis, autoimmune diseases…..etc***(Gigante, et al., 2014)***

In both ADHF and acute myocardial infarction (AMI), the development of WRF/AKI has been associated with worse clinical outcomes and higher health care costs ***(Aldeeb,et al., 2014).***

In ADHF, the presence of AKI confers an increased risk for both short-term and long-term mortality. Moreover, there appears to be a biological gradient seen between severity of AKI and risk of death, Two studies have shown that the risk of poor outcome persisted regardless of whether WRF/AKI was transient or sustained, Several studies have shown that the development of AKI in association with ADHF prolongs stay in hospital, While two studies showed that AKI in ADHF was associated with increased readmission rates this was not a universal finding***(Glassock, et al.,2010) .***

Similar to ADHF, AKI associated with ACS appears to significantly modify the risk of poor outcome, Importantly, even small acute changes in SCr appear to modify the risk of death .

In addition, data have also suggested a greater occurrence of cardiovascular events such as congestive heart failure (CHF), recurrent ACS and stroke and need for re-hospitalization among patients who developed AKI ***(Newsome, et al.,2012).***

Newsome reported a greater likelihood and/or rate of progression to end-stage kidney disease (ESKD) in those with ACS complicated by AKI . These data would suggest that the development of AKI in association with ADHF or ACS may further exacerbate cardiac injury and/or function and also contribute to exaggerated declines in kidney function. This would imply that the observed heart–kidney interface in Type 1 CRS may synergistically act to further accelerate injury and/or dysfunction following the initial insult ***(levey, et al.,2012).***

Eventhough in type 5 CRS 2 patients died from lupus nephritis and intra alveolar haemorrhage, other 2 patients died from acute septicemia and DIC *(P value 0.001).*

The prototypical condition that may lead to acute Type 5 CRS is sepsis. Sepsis occurs at a rate of three cases per 1000 population and is increasing by an estimated 8.7%/year.The case fatality remains high and estimated to be between 20 and 60%, a rate comparable to the annual mortality for AMI . While data have suggested a declining trend in mortality, the absolute number of patients dying from sepsis has increased . Approximately 11–64% of septic patients develop AKI and 46–58% have sepsis as a major contributing factor to the development of AK. Numerous studies have shown higher morbidity and mortality for those with septic AKI when compared to those with either sepsis or AKI alone . Similarly,

abnormalities in cardiac function are common in critically ill patients with sepsis***(Sporn,et al.,2011)*** **.**

The incidence of cardiac dysfunction in sepsis is conditional on the population-at-risk being studied, the definition used for the detection of cardiac dysfunction (i.e. troponin elevation, B-type natriuretic peptide, low cardiac output by pulmonary artery catheter, left ventricular dysfunction by echocardiography), severity of illness, resuscitation and duration of illness prior to evaluation. However, observational data have found that approximately 30–80% have elevated cardiac-specific troponins that often correlate with reduced cardiac function. Acute kidney and myocardial dysfunction in sepsis are accordingly common, yet there is a lack of integrative and epidemiologic studies that have specifically examined for insight on the pathophysiology, incidence, risk identification and associated outcomes for septic patients with concomitant AKI and myocardial depression who may fulfill the criteria for acute Type 5 CRS***(young, et al.,2008).***

In Benha university hospitals we studied the effect of CRS on the duration of hospital stay where 11.1 % of type 1 CRS patients showed increase in the duration of hospital stay by 15 days more as compared with those patients without AKI, type 2 (47.4%) increase in hospital stay days, type 3 (53.9%), type 4 (60.8%) and type 5 (63.9%) *(p value .001).*

The prevalence of CRS showed a wide variation between different departments in Benha university hospitals with type 1 CRS being higher in coronary care unit (51.9%), in ICU (22.2%), cardiothoracic surgery (11.1%), internal medicine and chest departments (7.4%).

Type 2 CRS showed highest prevalence in internal medicine department (55.3%), cardiology (32.9%), chest department (5.3%), ICU department (4%) and cardiothoracic surgery department (2.6%).

The prevalence of CRS type 3 was highest in ICU department (46.2%), internal medicine (38.5%) and cardiology department (15.4%).

Type 4 CRS was highest in internal medicine department (84.3%), ICU department (9.8%), cardiology department (3.9%) and cadiothoacic surgery (2%).

Finally the prevalence of type 5 CRS was highest in internal medicine department (54.2%) , cardiology department (19.3%), ICU department (12.1%) ,Rheumatology department (12.1%) and chest department (2.4%)*(P value 0.001)*.

This study included the most common causes of different types of CRS, type 1 CRS the most common causes of ADHF was as follows pneumonia (44.4%), ACS (29.6%), severe HTN (14.8%), pulmonary embolism (7.4%) and cardiac tamponade (3.7%).

Type 2 CRS the most common causes of chronic heart failure were dilated cardiomyopathy (43.4%), ischaemic cardiomyopathy (30.3%) and rheumatic heart disease (26.3%).

Older patients, diabetics and those who have been receiving a longer duration of maintenance RRT (>3.7 years) had higher prevalence of cardiac disease. During follow-up, 39.8% of enrolled patients were admitted to hospital for cardiac-related diagnoses. Of these, 42.7% were

attributable to ischaemic CHD. Of the 39.4% of cardiac deaths, 61.5% were attributable to ischaemic CHD***(Ronco, et l.,2004).***

Baseline cardiac disease was significantly predictive of cardiac-specific death during follow-up (relative risk 2.57). Cardiac disease in ESKD patients is exceedingly common, and cardiac-specific mortality rates are 10–20-fold higher when compared with age- and sex-matched non-CKD populations . Moreover, recent data have emerged to suggest dialysis prescription in selected patients with ESKD receiving chronic maintenance dialysis may precipitate cardiac injury and contribute to accelerated declines in myocardial performance Type 3 CRS the most common causes of AKI was ischaemic ATN, nephrotoxic ATN, obstructive uropathy and acut GN with the following percentage respectively 38.5%, 15.4% , 15.4% ,30.7%.

Type 4 CRS the most common causes of CKD was as follows chronic GN (27.5%), analgesic nephropathy (23.5%) , chronic interstitial nephritis(3.9%) and (41.2%) were on regular dialysis and (3.9%) APKD.

Finally type 5 CRS the systemic causes affecting heart and kidney was DM (51.8%), HTN (38.6%), SLE(6%) and acute septicemia(3.6%).

Summery

The cardiorenal syndrome is a clinicopathologic disorder in which a primary insult in the kidney or the heart initiates a series of secondary functional and morphological responses in the other organ (Herzog et al, 2007).

Cardiorenal syndrome is divided by Ronco (2008), et al **into five**

subtypes:

Type 1**: acute cardiorenal syndrome in which acute decompensated heart failure leads to acute kidney injury.**

Type 2: **chronic cardiorenal syndrome in which chronic heart failure leads to chronic kidney disease.**

Type 3: **acute renocardiac syndrome in which acute kidney injury leads to acute cardiac dysfunction as arrhythmia or heart failure.**

Type 4: **chronic renocardiac syndrome in which primary chronic kidney disease contributes to cardiac dysfunction.**

Type 5: **secondary cardiorenal syndrome in which cardiac and renal dysfunction occurs secondary to a systemic disease such as sepsis or SLE** (Ronco et al., 2008).

The kidney receives 20% of cardiac output so the heart and the kidney work interdependently so that changes in the volume and pressure in the cardiac atria initiate reflexes that alter the renal function (Hillege HD et al., 2006).

Increase in the left atrial pressure is associated with suppression of antidiuretic hormone and arginine vasopressin (Henry Gauer reflex), this reflex is mediated via the vagus nerve so vagotomy abolishes this reflex, this reflex is

responsible for the water diuresis following paroxysmal atrial tachycardia (Meyer et al, 2008).

De Bold (1945) observed granules in the cardiac atria when theses granules injected in rats they produced a profound increase in urinary sodium and water, these granules contain a hormone called atrial natriuretic peptide that produces suppression of RAAS system and sympathetic neural activity producing systemic and renal vasodilatation (Josep et al, 2008).

The cardiac ventricles contain a similar substance called the brain Natriuretic peptide as it is first found in the brain.

More than 30% of the overall acute decompensated heart failure patients develop renal dysfunction (Bongartz LG et al, 2005).

Cardiovascular disease is common in CKD with 43.6% of all, deaths in patients with ESRD due to cardiac cause (Geisberg et al, 2006)

Type 1 **cardiorenal syndrome acute kidney injury appears to be more severe in patients with decreased left ventricular ejection fraction compaired with normal left ventricular ejection fraction achieving incidence of 70% in patients with cardiogenic shock** (Shale et al, 2006).

The prevalence Of renal dysfunction in chronic heart failure has been reported to be 25% (Hostetter et al, 2007).

Type 3 **acute renocardiac syndrome ,the acute kidney injury can produce fluid overload and left sided heart failure, also hyperkalemia can cause arrhythmias and even cardiac arrest, untreated uraemia and acidosis produces impaired cardiac contractility** (Henry et ah, 2009).

Type 5 **secondary cardiorenal syndrome,severe sepsis is the most common and serious condition affecting both organs** (Haapio et aL, 2008).

References

1. **Abbate M, Zoja C & Remuzzi G (2006)** : How does proteinuria cause progressive renal damage? J Am Soc Nephrol; 17: 2974–2984.
2. **Abraham WT (2005) :** In-hospital mortalityin patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol;46(1):57–64.
3. **Adams Jr K.F., G.C. Fonarow& C.L. Emerman** (2005) :Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the acute decompensated heart failure national registry (ADHERE), Am Heart J, 149 pp. 209–216
4. **Adams KF Jr (** 2005) :Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J;149(2):209–16.
5. **Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M& Horton DP** (2005) : for the ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J.; 149: 209–216.
6. **Adler, Eric D.; Goldfinger, Judith Z.; Kalman, Jill; Park& Michelle E.; Meier, Diane E (**2014) **:** "Palliative Care in the Treatment of Advanced Heart Failure". American Heart Association Journals. doi:10.1161/ CIRCULATIONAHA. 109.869123. Retrieved 8 July.
7. **Agarwal M, Selvan V, Freedman BI, Liu Y& Wagenknecht LE**(2005): The relationship between albuminuria and hormone therapy in postmenopausal women. Am J Kidney Dis, 45:1019-1025.
8. **Ahmed A** (2006**) :** Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. Eur Heart J;27(12):1431–9.
9. **Al Deeb, M; Barbic, S; Featherstone, R; Dankoff, J& Barbic D** (August 2014). "Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: a systematic review and meta-analysis.". Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 21 (8): 843–52. doi:10.1111/acem.12435. PMID 25176151.

10. **Al Suwaidi J., D.N. Reddan& K. Williams**(2002): Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation, 106 pp. 974–980

11. **Al-Ahmad, W.M. Rand& G. Manjunath**(2001): Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol, 38 pp. 955–962

12. **Alfrey AC.** The role of abnormal phosphorus metabolism in the progression of chronic kidney disease and metastatic calcification. Kidney Int Suppl 2004; 66: S13–S17.

13. **Almeshari K., N.G**. **Ahlstrom, F.E. Caprar C.S& Wilcox**(1993):A volume-independent component to postdiuretic sodium retention in humans, J Am Soc Nephrol, 3 pp. 1878–1883

14. **Alves TP, Hulgan T, Wu P, Sterling TR, Stinnette SE, Rebeiro PF, Vincz AJ, Bruce M& Ikizler TA(**2010): Race, kidney disease progression, and mortality risk in HIV-infected persons. Clin J Am Soc Nephrol, 5:2269-2275.

15. **Anavekar N.S., J.J. McMurra& E.J. Velazquez**(2004): Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med, 351 pp. 1285–1295

16. **Andersen PK, Geskus RB, de Witte T& Putter H(**2012): Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol, 41:861-870.

17. **Andreev, E, Koopman, M, and Arisz, L**(1999**):** A rise in plasma creatinine that is not a sign of renal failure: which drugs can be responsible?. J Intern Med.; 246: 247–252

18. **Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K&Drexler H**(2009**):** Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med.;361:2436–2448.

19. **Appel GB, Radhakrishnan J& Avram MM** (2003**):** Analysis of metabolic parameters as predictors of risk in the RENAAL study. Diabetes Care; 26: 1402–1407.

20. **Appel LJ, Wright Jr JT& Greene T** (2010**):** Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med; 363: 918–929.

21. **Arcasoy M.O**(2007): Erythropoietin protects cardiac myocytes against anthracycline-induced apoptosis. Biochem Biophys Res Commun, 354 pp. 372–378

22. **Armendariz-Borunda J, Islas-Carbajal MC& Meza-Garcia E**(2006**) :** A pilot study in patients with established advanced liver fibrosis using pirfenidone. Gut; 55: 1663–1665.

23. **Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R& Berg KJ**. (2003):Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic eff ects in high-risk patients undergoing angiography. N Engl J Med; 348: 491–99.

24. Astor BC, Lewis J, Hu B, Appel LJ, Lipkowitz MS, Toto RD, Wang X, Wright JTJ& Greene TH (2012): Longitudinal progression trajectory of GFR among patients with CKD. Am J Kidney Dis, 59:504-512.

25. **Auble TE, Hsieh M, McCausland JB& Yealy DM (2007):** "Comparison of four clinical prediction rules for estimating risk in heart failure". Annals of Emergency Medicine 50 (2): 127–35, 135.e1–2. doi:10.1016/j.annemergmed.2007.02.017. PMID 17449141.

26. Austin W.J., V. Bhalla, I. Hernandez-Arce(2006): Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. Am J Clin Pathol, 126 pp. 506–512

27. **Azuma A, Nukiwa T& Tsuboi E** (2005**)**: Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med; 171: 1040–1047.

28. **Babaei-Jadidi R, Karachalias N& Ahmed N** (2003**):** Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes; 52: 2110–2120.

29. Bachorzewska-Gajewska H., J. Malyszko, E. Sitniewska, J.S. Malyszko S. &Dobrzycki(2006):Neutrophil-gelatinase-associated lipocalin and renal function after percutaneous coronary interventions. Am J Nephrol, 26 pp. 287–292

30. **Badgett RG& Lucey CR**(1997): Mulrow CD. Can the clinical examination diagnose left-sided heart failure in adults? Jama;277(21):1712–9.

31. Bagshaw S.M., A. Delaney, M. Haase, W.A. Ghali& R. Bellomo(2007): Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis, Crit Care Resusc, 9, pp. 60–68

32. **Bagshaw SM& Bellomo R**(2010):Urine abnormalities in acute kidney injury and sepsis. Contrib Nephrol; 165: 274–83.

33. **Bagshaw SM, Berthiaume LR, Delaney A& Bellomo R**(2008): Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med; 36: 610–17.

34. **Bagshaw SM, Cruz DN, Gibney RT& Ronco C**(2009)**:** A proposed algorithm for initiation of renal replacement therapy in adult critically ill patients. Crit Care; 13: 317.

35. **Bagshaw SM, Delaney A, Haase M, Ghali WA& Bellomo R**(2007): Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. Crit Care Resusc; 9: 60–68.

36. **Bagshaw SM& Gibney RT** (2009**):** Acute kidney injury: clinical value of urine microscopy in acute kidney injury. Nat Rev Nephrol; 5: 185–86.

37. **Baigent C& Landray MJ, Reith C (**2011**):** The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet; 377: 2181–2192.

38. Bakris G.L., M.R(2000): Weir. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med, 160, pp. 685–693

39. **Bakris GL, Hart P& Ritz E**. (2006)**.** Beta blockers in the management of chronic kidney disease. Kidney Int;70:1905–1913.

40. **Baldasseroni S; Opasich C; Gorini M& Lucci D** (2002): "Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure". American Heart Journal 143 (3): 398–405. doi:10.1067/mhj.2002.121264. PMID 11868043.

41. **Baliga RR(**2006**):** Spironolactone treatment and clinical outcomes in patients with systolic dysfunction and mild heart failure symptoms: a retrospective analysis. J Card Fail; 12(4):250–6.

42. **Basu, A, Devaraj, S, and Jialal I**(2006**):** Dietary factors that promote or retard inflammation. Arterioscler Thromb Vasc Biol. 2006 May; 26: 995–1001 (Epub Feb 16.)

43. **Bayliss EA, Bhardwaja B& Ross C** (2011**):**Multidisciplinary team care may slow the rate of decline in renal function. Clin J Am Soc Nephrol.

44. Beattie J.N., S.S. Soman, K.R. Sandberg(2001): Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. Am J Kidney Dis, 37 pp. 1191–1200

45. **Begun A, Icks A, Waldeyer R, Landwehr S, Koch M& Giani G**(2013)**:** Identification of a multistate continuous-time nonhomogeneous markov chain model for patients with decreased renal function. Med Decis Making, 33:298-306.

46. **Bell M; SWING, Granath F, Schon S,** Ekbom A& Martling CR(2007): Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med; 33: 773–80.

47. **Bellasi A, Mandreoli M& Baldrati L (**2011**)**: Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-moderate kidney dysfunction. Clin J Am Soc Nephrol; 6: 883–891.

48. **Bellomo R, Bagshaw SM, Langenberg C& Ronco C**(2007**)** Pre-renal azotemia: a fl awed paradigm in critically ill septic patients? Contrib Nephrol; 156: 1–9.

49. **Bellomo R, Bonventre J& Macias W**(2005**):**Pinsky M. Management of early acute renal failure: focus on post-injury prevention. Curr Opin Crit Care; 11: 542–47.

50. **Bellomo R, Ronco C, Kellum JA, Mehta RL&Palevsky P**(2004**):** and the Acute Dialysis Quality Initiative workgroup. Acute renal failure— definition, outcome measures, animal models, fl uid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative Group. Crit Care; 8: R204–R12.

51. **Bellomo R, Tetta C& Ronco C**(2003**)**: Couple plasma fi ltration adsorption. Intensive Care Med; 29: 1222–28.

52. Bellomo R., C. Ronco, J.A. Kellum, R.L. Mehta, P& Palevsky(2004):Acute Dialysis Quality Initiative Workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) group. Crit Care, 8 pp. R204–R212

53. **Bentley ML, Corwin HL& Dasta J**(2010)**:** Drug-induced acute kidney injury in the critically ill adult: recognition and prevention strategies. Crit Care Med; 38 (suppl 6): S169–74.

54. **Berger A.K., S. Duval& H.M. Krumholz**(2003): Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol, 42, pp. 201–208

55. **Best PJ, Steinhubl SR, Berger PB, Dasgupta A, Brennan DM& Szczech LA**(2008**):** The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Am Heart J.;155:687–693.

56. Bhatia R.S., J.V. Tu& D.S. Lee(2006): Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med, 355, pp. 260–269

57. **Bidani A**(2006**):** Controversy about COOPERATE ABPM trial data. Am J Nephrol; 26: 629, 632; author reply 629–632.

58. **Bielesz B, Sirin Y& Si H** (2010)**:**Epithelial Notch signaling regulates interstitial fibrosis development in the kidneys of mice and humans. J Clin Invest; 120: 4040–4054.

59. **Bilous R, Chaturvedi N, Sjolie AK, Fuller J, Klein R, Orchard T, Porta M& Parving HH**(2009)**:** Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann Intern Med, 151:11-20. W13-14

60. **Blake** P., Y. Hasegawa, M.C. Khosla, F. Fouad-Tarazi& N. Sakura, E.P(1996):Paganini. Isolation of "myocardial depressant factor(s)" from the ultrafiltrate of heart failure patients with acute renal failure. ASAIO J, 42 pp. M911–M915

61. **Blake WD, Wegria R, Keating RP& Ward HP**(1949)**.** Effect of increased renal venous pressure on renal function. Am J Physiol.; 157: 1–13.

62. **Blanche P, Dartigues JF& Jacqmin-Gadda H**(2013)**:** Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Stat Med, 32:5381-5397.

63. **Bolton WK, Cattran DC& Williams ME** (2004)**:** Randomized trial of an inhibitor of formation of advanced glycation end products in diabetic nephropathy. Am J Nephrol; 24: 32–40.

64. **Bomback AS, Kshirsagar AV& Amamoo MA** (2008)**:** Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis; 51: 199–211.

65. ***Bongartz LG***(1996):Isolation of "myocardial depressant factor(s)" from the ultrafiltrate of heart failure patients with acute renal failure. ASAIO J, 42 pp. M911–M915

66. **Boron, Walter F.; Boulpaep& Emile L. (2005):** Medical Physiology: A Cellular and Molecular Approach (Updated ed.). Saunders. p. 533. ISBN 0-7216-3256-4.

67. **Bradley SE& Bradley GP**(1947)**:** The effect of increased intra-abdominal pressure on renal function in man. J Clin Invest.; 26: 1010–1015.

68. Brady J.P& J.A. Hasbargen(2000):A review of the effects of correction of acidosis on nutrition in dialysis patients. Semin Dial, 13 pp. 252–255

69. **Brar SS, Shen AY& Jorgensen MB(**2008)**:** Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. JAMA; 300: 1038–46.

70. **Braunwald. Biomarkers in heart failure**(2008): N Engl J Med, 358 pp. 2148–2159

71. **Brenner BM, Cooper ME&** de Zeeuw D (2001): Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med; 345: 861–869.

72. **Brochu E, Lacasse S& Moreau C** (1999**):** Endothelin ET(A) receptor blockade prevents the progression of renal failure and hypertension in uraemic rats. Nephrol Dial Transplant; 14: 1881–1888.

73. **Brownlee M, Vlassara H& Kooney A** (1986**):** Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking. Science; 232: 1629–1632.

74. Brunkhorst F.M., C. Engel& F. Bloos(2008): Intensive insulin therapy and pentastarch resuscitation in severe sepsis, N Engl J Med, 358 pp. 125–139

75. **Bui, AL; Horwich, TB; Fonarow& GC (January 2011):** "Epidemiology and risk profile of heart failure.". Nature Reviews Cardiology 8 (1): 30–41. doi:10.1038/nrcardio.165. PMC 3033496. PMID 21060326.

76. **Burton P, Gurrin L& Sly P**(1998)**:** Extending the simple linear regression model to account for correlated responses: an introduction to generalized estimating equations and multi-level mixed modelling. Stat Med, 17:1261-1291.

77. Butler J., D.E. Forman, W.T& Abraham(2004): Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J, 147, pp. 331–338

78. **Calvillo L, Latini R, Kajstura J, Leri A, Anversa P, Ghezzi P, Salio M, Cerami A& Brines M**(2003)**:** Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling. Proc Natl Acad Sci U S A.; 100: 4802–4806.

79. Cameron S.J., L.J. Sokoll, O.F. Laterza, S. Shah& G.B. Green(2007): A multi-marker approach for the prediction of adverse events in patients with acute coronary syndromes. Clin Chim Acta, 376 pp. 168–173

80. **Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria**(1996**).** The Microalbuminuria Captopril Study Group. Diabetologia; 39: 587–593.

81. Carr S.J., S. Bavanandan, B. Fentum& L. Ng(2005):Prognostic potential of brain natriuretic peptide (BNP) in predialysis chronic kidney disease patients. Clin Sci (Lond), 109 pp. 75–82

82. Carrel, T; Englberger, L; Martinelli, MV; Takala, J; Boesch, C; Sigurdadottir, V; Gygax, E; Kadner, A& Mohacsi, P (Oct 18, 2012):"Continuous flow left ventricular assist devices: a valid option for heart failure patients.". Swiss medical weekly 142: w13701. doi:10.4414/smw.2012.13701. PMID 23135811.

83. Cazzavillan S., R. Ratanarat& C. Segala(2007): Inflammation and subclinical infection in chronic kidney disease: a molecular approach. Blood Purif, 25 pp. 69–76

84. Chait A(1972): The bedside chest radiograph in the evaluation of incipient heart failure. Radiology;105(3):563–6.

85. Chakko S(1991): Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. Am J Med;90(3):353–9.

86. Chandra D(2007): Usefulness of percutaneous left ventricular assist device as a bridge to recovery from myocarditis. Am J Cardiol;99(12):1755–6.

87. Chapman AB(2008) Approaches to testing new treatments in autosomal dominant polycystic kidney disease: insights from the CRISP and HALT-PKD studies. Clin J Am Soc Nephrol; 3: 1197–1204.

88. Chen SC, Hwang SJ& Tsai JC (2010): Early nephrology referral is associated with prolonged survival in hemodialysis patients even after exclusion of lead-time bias. Am J Med Sci; 339: 123–126.

89. Chen **Z.M., H.C. Pan& Y.P. Chen**(2005):Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet, 366 pp. 1622–1632

90. Chen, C. Assad-Kottner& C. Orrego, G(2008): Torre-Amione. Cytokines and acute heart failure. Crit Care Med, 36 pp. S9–S16

91. **Chertow G.M., D. Fan, C.E. McCulloch& C.Y. Hsu**(2004): Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med, 351, pp. 1296–1305.

92. Chertow GM& Fan D (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med; 351: 1296–1305.

93. Cheuk-Man Yu; Wang, Li; Chau, Elaine; Chan, Raymond Hon-Wah; Kong, Shun-Ling; Tang& Man-Oi (1 August 2005): "Correlation With Fluid Status and Feasibility of Early Warning Preceding Hospitalization". American Heart Association Journals. doi:10.1161/CIRCULATIONAHA.104.492207. Retrieved 8 July 2005.

94. Cho ME, Smith DC& Branton MH (2007):Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. Clin J Am Soc Nephrol; 2: 906–913.

95. Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care(2010): Partial Update". National Clinical Guideline Centre: 34–47. Aug. PMID 22741186.

96. Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care(2010): Partial Update". National Clinical Guideline Centre: 71–153. Aug. PMID 22741186.

97. Cianciaruso B, Pota A, Bellizzi V, Di Giuseppe D, Di Micco L, Minutolo R, Pisani A, Sabbatini M& Ravani P(2009): Effect of a low- versus moderate-protein diet on progression of CKD: follow-up of a randomized controlled trial. Am J Kidney Dis, 54:1052-1061.

98. **Collins A.J., S. Li, D.T. Gilbertson, J. Liu, S.C. Chen& C.A. Herzog**(2003): Chronic kidney disease and cardiovascular disease in the Medicare population. Kidney Int Suppl, 87 pp. S24–S31

99. Colucci WS(2000): Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N Engl J Med;343(4):246–53.

100. Coresh J, Astor BC, Greene T, Eknoyan G& Levey AS(2003): Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis.; 41: 1–12.

101. Coresh J., B.C. Astor, T. Greene, G. Eknoyan& A.S. Levey(2003): Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis, 41 pp. 1–12

102. Corteville DC(2007): N-terminal pro-B-type natriuretic peptide as a diagnostic test for ventricular dysfunction in patients with coronary disease: data from the heart and soul study. Arch Intern Med;167(5):483–9.

103. Costanzo MR(2007): Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol;49(6):675–83.

104. Costanzo MR, Guglin ME& Saltzberg MT(2007): Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 13;49:675–83.

105. CostanzoMR(2007): Thesafetyofintravenousdiuretics alone versus diuretics plus parenteral vasoactivetherapiesin hospitalized patientswith acutelydecompensated heart failure: a propensity score and instrumental variable analysis using the Acutely Decompensated Heart Failure National Registry (ADHERE) database. Am Heart J;154(2):267–77.

106. Coxib and traditional NSAID Trialists' (CNT), Collaboration; Bhala, E; Hawkey, C; Hennekens, C; Hochberg, M; Holland, LE; Kearney, PM; Laine, L; Lanas, A; Lance, P; Laupacis, A; Oates, J; Patrono, C; Schnitzer, TJ; Solomon, S; Tugwell, P; Wilson, K; Wittes, J& Baigent, C (Aug 31, 2013):"Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.". Lancet 382 (9894): 769–79. doi:10.1016/S0140-6736(13)60900-9. PMC 3778977. PMID 23726390.

107. Criteria Committee, New York Heart Association (1964): Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis (6th ed.). Boston: Little, Brown. p. 114.

108. Cuffe MS(2002): Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. Jama;287(12):1541–7.

109. Cunningham P.N., H.M. Dyanov, P. Park, J. Wang, K.A. Newell& R.J. Quigg(2002): Acute renal failure in endotoxemia is caused by TNF acting directly on TNF receptor-1 in kidney. J Immunol, 168 pp. 5817–5823

110. Curhan GC, Mitch WE In& Brenner BM (2008):The Kidney, 8th edn. Saunders: Philadelphia, PA, , pp 1817–1847.

111. Curtis BM, Ravani P& Malberti F (2005) :The short- and long-term impact of multi-disciplinary clinics in addition to standard nephrology care on patient outcomes. Nephrol Dial Transplant; 20: 147–154.

112. Cushman WC, Evans GW& Byington RP (2001): Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362: 1575–1585.

113. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ& Hillege HL(2009): Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol; 53: 582–588.

114. Dao Q(2001): Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol;37(2):379–85.

115. Daroux M, Prevost G& Maillard-Lefebvre H (2010):Advanced glycation end-products: implications for diabetic and non-diabetic nephropathies. Diabetes Metab; 36: 1–10.

116. Dart AB, Mutter TC& Ruth CA(2010): Taback SP. Hydroxyethyl starch (HES) versus other fl uid therapies: eff ects on kidney function. Cochrane Database Syst Rev; 1: CD007594.

117. De Beaudrap P, Diallo MB, Landman R, Gueye NF, Ndiaye I, Diouf A, Kane CT, Etard JF, Girard PM, Sow PS& Delaporte E(2010): Changes in the renal function after tenofovir-containing antiretroviral therapy initiation in a Senegalese cohort (ANRS 1215). AIDS Res Hum Retroviruses, 26:1221-1227.

118. de Boer IH, Rue TC& Cleary PA (2005): Long-term Renal Outcomes of Patients With Type 1 Diabetes Mellitus and Microalbuminuria: An Analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort. Arch Intern Med 171: 412–420.

119. de Brito-Ashurst I, Varagunam M& Raftery MJ (2009): Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol; 20: 2075–2084.

120. De Nicola L, Minutolo R, Chiodini P, Zamboli P, Cianciaruso B, Nappi F, Signoriello S, Conte G& Zoccali C(2010): Group S-TCS: Prevalence and prognosis of mild anemia in non-dialysis chronic kidney disease: a prospective cohort study in outpatient renal clinics. Am J Nephrol, 32:533-540.

121. De Wreede LC, Fiocco M& Putter H (2011): mstate: An R package for the analysis of competing risks and multi-state models. J Stat Softw, 38:1-30.

122. de Zeeuw D, Agarwal R, Amdahl M :Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet 376: 1543–1551.

123. Degenhardt TP, Alderson NL& Arrington DD (2002): Pyridoxamine inhibits early renal disease and dyslipidemia in the streptozotocin-diabetic rat. Kidney Int; 61: 939–950.

124. Devarajan P, Krawczeski CD, Nguyen MT, Kathman T, Wang Z& Parikh CR(2010): Proteomic identifi cation of early biomarkers of acute kidney injury after cardiac surgery in children. Am J Kidney Dis; 56: 632–42.

125. Devarajan P., J. Mishra, S. Supavekin, L.T. Patterson& S. Steven Potter(2003):Gene expression in early ischemic renal injury: clues towards pathogenesis, biomarker discovery, and novel therapeutics. Mol Genet Metab, 80 pp. 365–376.

126. Devins GM, Mendelssohn DC& Barre PE (2003): Predialysis psychoeducational intervention and coping styles influence time to dialysis in chronic kidney disease. Am J Kidney Dis; 42: 693–703.

127. Dharnidharka V.R., C. Kwon& G. Stevens(2002):. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis, 40 (), pp. 221–226

128. Dhaun N, Goddard J& Webb DJ(2006): The endothelin system and its antagonism in chronic kidney disease. J Am Soc Nephrol; 17: 943–955.

129. Dickstein K, Cohen-Solal A& Filippatos G (October 2008): "ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)". Eur. Heart J. 29 (19).

130. Dinicolantonio, JJ; Pasquale, PD; Taylor, RS& Hackam, DG (Jan 24, 2013): "Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis.". Heart (British Cardiac Society). doi:10.1136/heartjnl-2012-302337..

131. Doty JM, Saggi BH, Blocher CR, Fakhry I, Gehr T, Sica D& Sugerman HJ(2000). Effects of increased renal parenchymal pressure on renal function. J Trauma.; 48: 874–877.

132. Douglas K, O′Malley PG& Jackson JL(2006): Meta-analysis: the effect of statins on albuminuria. Ann Intern Med; 145: 117–124.

133. Drazner MH(2001): Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med;345(8):574–81.

134. Drazner MH, Rame JE, Stevenson LW& Dries DL(2001): Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med.; 345: 574–581.

135. Duffield J.S., S. Hong& V.S. Vaidya(2006): Resolvin D series and protectin D1 mitigate acute kidney injury. J Immunol, 177, pp. 5902–5911

136. Duke G.J., Renal protective agents: a review, Crit Care Resusc, 1 (1999): pp. 265–275

137. Dussol B, Moussi-Frances J& Morange S (2005): A randomized trial of furosemide vs hydrochlorothiazide in patients with chronic renal failure and hypertension. Nephrol Dial Transplant 20: 349–353.

138. Dworzynski, K; Roberts, E; Ludman, A; Mant, J; Guideline Development, Group (8 October 2014):"Diagnosing and managing acute heart failure in adults: summary of NICE guidance.". BMJ (Clinical research ed.) 349: g5695. doi:10.1136/bmj.g5695. PMID 25296764.

139. Eddington H, Hoefield R& Sinha S (2003): Serum phosphate and mortality in patients with chronic kidney disease. Clin J Am Soc Nephrol 5: 2251–2257.

140. Effect of metoprolol CR/XL in chronic heart failure(1999): Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet;353(9169):2001–7.

141. Ejection Fraction Heart Failure Measurement. American Heart Association. Feb 11, 2014. Retrieved 7 June 2014.

142. Ejection Fraction. Heart Rhythm Society. Retrieved 7 June 2014.

143. Elixhauser A, Steiner C. Readmissions to U.S. Hospitals by Diagnosis, (2010): HCUP Statistical Brief #153. Agency for Healthcare Research and Quality. April 2013.

144. Elkayam U(2004): Comparison of effects on left ventricular filling pressure of intravenous nesiritide and high-dose nitroglycerin in patients with decompensated heart failure. Am J Cardiol;93(2):237–40.

145. Elkayam U(2007): Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. Am Heart J;153(1):98–104.

146. Ellison D.H. Diuretic resistance(1999): physiology and therapeutics. Semin Nephrol, 19 pp. 581–597

147. Endre, Z., & Westhuyzen, J. (2008): Early detection of acute kidney injury: emerging new biomarkers. Nephrology, 13(2):91-98.

148. Eriksen BO, Tomtum J& Ingebretsen OC(2010): Predictors of declining glomerular filtration rate in a population-based chronic kidney disease cohort. Nephron Clin Pract, 115:c41-50.

149. Espinel, CH(1976): The FENa test: use in the differential diagnosis of acute renal failure. JAMA.; 236: 579–581

150. Evans M, Fored CM, Bellocco R, Fitzmaurice G, Fryzek JP, McLaughlin JK, Nyren O& Elinder CG(2009): Acetaminophen, aspirin and progression of advanced chronic kidney disease. Nephrol Dial Transplant, 24:1908-1918.

151. Ewald B, Ewald D, Thakkinstian A& Attia J (2008): "Meta-analysis of B type natriuretic peptide and N-terminal pro B natriuretic peptide in the diagnosis of clinical heart failure and population screening for left ventricular systolic dysfunction". Intern Med J 38 (2): 101–13. doi:10.1111/j.1445-5994.2007.01454.x. PMID 18290826.

152. Falagas ME, Pitsouni EI, Malietzis GA& Pappas G(2008): Comparison of , Scopus, Web of Science, and Google Scholar: strengths and weaknesses. FASEB J, 22:338-342.

153. Falk RJ& Jennette JC(2010): ANCA disease: where is this fi eld heading? J Am Soc Nephrol; 21: 745–52.

154. Faris, RF; Flather, M; Purcell, H; Poole-Wilson, PA; Coats& AJ (Feb 15, 2012): "Diuretics for heart failure.". The Cochrane database of systematic reviews 2: CD003838. doi:10.1002/14651858.CD003838.pub3. PMID 22336795.

155. Feehally J, Floege J, Savill J& Turner AN (2005): Glomerular injury and glomerular response. In: Davison AM, ed. Oxford textbook of clinical nephrology. Oxford: Oxford University Press: 363–87.

156. Feig DI, Kang DH& Johnson RJ(2008): Uric acid and cardiovascular risk. N Engl J Med; 359: 1811–1821.

157. Felker GM, (2003):Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol;41(6):997–1003.

158. Feltner, C; Jones, CD; Cené, CW; Zheng, ZJ; Sueta, CA; Coker-Schwimmer, EJ; Arvanitis, M; Lohr, KN; Middleton, JC& Jonas, DE (Jun 3, 2014): "Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis.". Annals of internal medicine 160 (11): 774–84. doi:10.7326/M14-0083. PMID 24862840.

159. Fiaccadori E, Parenti E& Maggiore U(2008): Nutritional support in acute kidney injury. J Nephrol; 21: 645–56.

160. Figarola JL, Loera S& Weng Y (2008): LR-90 prevents dyslipidaemia and diabetic nephropathy in the Zucker diabetic fatty rat. Diabetologia; 51: 882–891.

161. Figueras J., L. Stein, V. Diez& M.H. Weil, H(1976): Shubin. Relationship between pulmonary hemodynamics and arterial pH and carbon dioxide tension in critically ill patients. Chest, 70 pp. 466–472

162. Fisher, SA; Brunskill, SJ; Doree, C; Mathur, A; Taggart, DP& Martin-Rendon, E (Apr 29, 2014): "Stem cell therapy for chronic ischaemic heart disease and congestive heart failure.". The Cochrane database of systematic reviews 4: CD007888. doi:10.1002/14651858.CD007888.pub2. PMID 24777540.

163. Fitzmaurice G, Davidian M, Verbeke G&Molenberghs G(2009): Longitudinal data analysis. Chapman & Hall/CRC: Boca Raton, USA;.

164. Fliser D, Kollerits B& Neyer U (2007): Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol; 18: 2600–2608.

165. Foley R.N., P.S. Parfrey& M.J. Sarnak(1998):Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis, 32 pp. S112–S119

166. Foley RN(2009);. Phosphate levels and cardiovascular disease in the general population. Clin J Am Soc Nephrol 4: 1136–1139.

167. Fonarow G.C., W.G. Stough& W.T. Abraham(2007): Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry, J Am Coll Cardiol, 50 pp. 768–777

168. Fonarow GC, Abraham WT& Albert NM (April 2008): "Factors Identified as Precipitating Hospital Admissions for Heart Failure and Clinical Outcomes: Findings From OPTIMIZE-HF". Arch. Intern. Med. 168 (8): 847–854. doi:10.1001/archinte.168.8.847. PMID 18443260.

169. Fonarow GC(2005): Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. Jama;293(5):572–80.

170. Fonarow GC(2007): Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J;153(6):1021–8.

171. Fonarow GC(2003): The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med;(4 Suppl 7):S21–30.

172. Forfia P.R., M. Lee, R.S. Tunin, M. Mahmud, H.C. Champion& D.A. Kass(2007): Acute phosphodiesterase 5 inhibition mimics hemodynamic effects of B-type natriuretic peptide and potentiates B-type natriuretic peptide effects in failing but not normal canine heart. J Am Coll Cardiol, 49, pp. 1079–1088

173. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB& Krumholz HM(2004): Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol.; 43: 61–67.

174. Forsblom C, Harjutsalo V, Thorn LM, Waden J, Tolonen N, Saraheimo M, Gordin D, Moran JL, Thomas MC& Groop PH(2011): Competing-risk analysis of ESRD and death among patients with type 1 diabetes and macroalbuminuria. J Am Soc Nephrol, 22:537-544.

175. Foucher Y, Giral M, Soulillou JP& Daures JP(2010): A flexible semi-Markov model for interval-censored data and goodness-of-fit testing. Stat Methods Med Res, 19:127-145.

176. Fouque D& Laville M(2009):. Low protein diets for chronic kidney disease in non diabetic adults. Cochrane Database Syst Rev CD001892.

177. Fouque, D and Aparicio, M(2007): Eleven reasons to control the protein intake of patients with chronic kidney disease. Nat Clin Pract Nephrol.; 3: 383–392

178. Francis GS(2004): Acute heart failure: patient management of agrowing epidemic. Am Heart Hosp J;2 (4 Suppl. 1):10–4.

179. French W.J& R.S(2003): Wright. Renal insufficiency and worsened prognosis with STEMI: a call for action. J Am Coll Cardiol, 42 pp. 1544–1546

180. Fried LF, Duckworth W& Zhang JH (2009): Design of combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor for treatment of diabetic nephropathy (VA NEPHRON-D). Clin J Am Soc Nephrol; 4: 361–368.

181. Funaya H, Kitakaze M, Node K, Minamino T, Komamura K&Hori M(1997): Plasma adenosine levels increase in patients with chronic heart failure. Circulation.; 95: 1363–1365.

182. Fung MM, Salem RM, Lipkowitz MS, Bhatnagar V, Pandey B, Schork NJ& O'Connor DT(2012): Methylenetetrahydrofolate reductase (MTHFR) polymorphism A1298C (Glu429Ala) Trial and Veterans Affairs Hypertension Cohort (VAHC). Nephrol Dial Transplant, 27:197-205.

183. Gal-Moscovici A& Sprague SM(2000): Use of vitamin D in chronic kidney disease patients. Kidney Int 78: 146–151.

184. Gandhi S.K., J.C. Powers& A.M. Nomeir(2001): The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med, 344 pp. 17–22

185. **Garg A.X., W.F. Clark, R.B& Haynes, A.A**(2002): House. Moderate renal insufficiency and the risk of cardiovascular mortality: Results from the NHANES I. Kidney Int, 61 pp. 1486–1494

186. Garre FG, Zwinderman AH, Geskus RB& Sijpkens YW(2008): A joint latent class changepoint model to improve the prediction of time to graft failure. J R Stat Soc Ser A Stat Soc, 171:299-308.

187. Garside R., M. Pitt, R. Anderson(2007): The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: A systematic review and economic evaluation. Health Technol Assess, 11 pp. 1–167 iii, xi, xiii

188. Gattis WA (2004): Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol;43(9):1534–41.

189. ***Geisberg*** (2007): Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J;28(8):980–8.

190. Genovese G, Friedman DJ, Ross MD (2010): Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science; 329: 841–845.

191. George J, Patal S, Wexler D, Abashidze A, Shmilovich H, Barak T. (2005):Circulating erythropoietin levels and prognosis in patients with congestive heart failure: comparison with neurohormonal and inflammatory markers. Arch Intern Med;165:1304–1309.

192. Ghali J.K., I.S. Anand, W.T. Abraham(2008): Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation, 117 pp. 526–535

193. Gheorghiade M(2007): Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J;28(8):980–8.

194. Gheorghiade M (2007): Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. Jama;297(12):1332–43.

195. Gheorghiade M., W.A. Gattis, C.M. O'Connor(2004): Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. JAMA, 291 pp. 1963–1971

196. **Gibson C.M., D.S. Pinto, S.A. Murphy**(2003): Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. J Am Coll Cardiol, 42 pp. 1535–1543

197. Glassock RJ. Debate(2010): CON position. Should microalbuminuria ever be considered as a renal endpoint in any clinical trial? Am J Nephrol; 31: 462–465; discussion 466–467.

198. Goddard J, Johnston NR, Hand MF (2004): Endothelin-A receptor antagonism reduces blood pressure and increases renal blood flow in hypertensive patients with chronic renal failure: a comparison of selective and combined endothelin receptor blockade. Circulation; 109: 1186–1193.

199. Goicoechea M, de Vinuesa SG, Verdalles U (2010): Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol; 5: 1388–1393.

200. Goldberg, H. Hammerman, S. Petcherski(2005): Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. Am Heart J, 150 (pp. 330–337

201. Goldman, Lee (2011): Goldman's Cecil Medicine: Heart Failure (Ch 58, 59) (24th ed.). Philadelphia: Elsevier Saunders. pp. 295–317. ISBN 1437727883.

202. Goldsmith SR, Francis GS, Cowley AW, Levine TB, Cohn JN. (1983): Increased plasma arginine vasopressin levels in patients with congestive heart failure, J Am Coll Cardiol; 1: 1385–1390.

203. Goldstein M, Yassa T, Dacouris N (2004): Multidisciplinary predialysis care and morbidity and mortality of patients on dialysis. Am J Kidney Dis; 44: 706–714.

204. Gottlieb S.S., D.C. Brater, I. Thomas(2002): et al. BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. Circulation, 105 (pp. 1348–1353

205. Gottlieb SS, Abraham WT, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM(2002): The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail.; 8: 136–141.

206. Grams ME, Coresh J(2013): Assessing risk in chronic kidney disease: a methodological review. Nat Rev Nephrol, 9:18-25.

207. Graves, JW(2007): The two best reasons NOT to focus on protein restriction in chronic kidney disease [letter]. Nat Clin Pract Nephrol.; 3: E1

208. Griendling KK, Minieri CA, Ollerensaw JD, Alexander RW(1994): Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res.; 74: 1141–1148.

209. Guijarro C, Kasiske BL, Kim Y (1995): Early glomerular changes in rats with dietary-induced hypercholesterolemia. Am J Kidney Dis; 26: 152–161.

210. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A(2009): Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis; 54: 1012–24.

211. Haase M, Haase-Fielitz A, Bellomo R, Mertens PR(2011): Neutrophil gelatinase-associated lipocalin as a marker of acute renal disease. Curr Opin Hematol; 18: 11–18.

212. Haldeman G.A., J.B. Croft, W.H. Giles, A. Rashidee, Hospitalization of patients with heart failure(1999): national hospital discharge survey, 1985 to 1995, Am Heart J, 137 pp. 352–360

213. Han S.W., Y.W. Won, J.H. Yi, H.J. Kim(2007): No impact of hyperkalaemia with renin-angiotensin system blockades in maintenance haemodialysis patients. Nephrol Dial Transplant, 22, pp. 1150–1155

214. Han W.K., J.V(2004): Bonventre. Biologic markers for the early detection of acute kidney injury. Curr Opin Crit Care, 10, pp. 476–482

215. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS(1995): Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int.; 47: 884–890.

216. Harrison A(2002): B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. Ann Emerg Med;39(2):131–8.

217. HasenfussG(1989): Myocardialenergetics in patientswith dilated-cardiomyopathy. Influence of nitroprusside and enoximone. Circulation;80(1):51–64.

218. He SW, Wang LX (2009): "The impact of anemia on the prognosis of chronic heart failure: a meta-analysis and systemic review". Congest Heart Fail 15 (3): 123–30. doi:10.1111/j.1751-7133.2008.00030.x. PMID 19522961.

219. Heidenhain R. Hermann's Handbuch der Physiologie, Volume 5. Leipzig, Germany(1883): F.C.W. Vogel;; I: 317.

220. Heidenreich PA(2005): ACE inhibitor reminders attached to echocardiography reports of patients with reduced left ventricular ejection fraction. Am J Med;118(9):1034–7.

221. Hemmelgarn BR, Manns BJ, Zhang J (2007): Association between multidisciplinary care and survival for elderly patients with chronic kidney disease. J Am Soc Nephrol; 18: 993–999.

222. Herget-Rosenthal S., G. Marggraf, J. Husing(2004): Early detection of acute renal failure by serum cystatin C. Kidney Int, 66, pp. 1115–1122

223. **Herzog C.A.** (2002): Dismal long-term survival of dialysis patients after acute myocardial infarction: can we alter the outcome? Nephrol Dial Transplant, 17 pp. 7–10

224. Heymes C, Bendall JK, Ratajczak P, Cave AC, Samuel JL, Hasenfuss G, Shah AM(2003): Increased myocardial NADPH oxidase activity in human heart failure. J Am Coll Cardiol.; 41: 2164–2171.

225. Hillege H.L., D. Nitsch, M.A. Pfeffer(2006): Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation, 113 pp. 671–678

226. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ(2000): Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation.; 102: 203–210.

227. Hines AL, Barrett ML, Jiang HJ, and Steiner CA. (April 2014): "Conditions With the Largest Number of Adult Hospital Readmissions by Payer, 2011.". HCUP Statistical Brief #172. Rockville, MD: Agency for Healthcare Research and Quality.

228. **Hirsch A.T., Z.J. Haskal, N.R. Hertzer**(2006): ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). J Am Coll Cardiol, 47 pp. e1–e192

229. Hjalmarson, S. Goldstein, B. Fagerberg, MERIT-HF Study Group(2000): Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). JAMA, 283 pp. 1295–1302

230. Hobbs FD, Kenkre JE, Roalfe AK, Davis RC, Hare R, Davies MK (December 2002): "Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population". Eur. Heart J. 23 (23): 1867–76. doi:10.1053/ euhj.2002.3255. PMID 12445536.

231. Hollenberg, NK. Treatment of the patient with diabetes mellitus and risk of nephropathy: what do we know, and what do we need to learn?. Arch Intern Med. 2004; 164: 125–130

232. Honore P.M., J. Jamez, M. Wauthier(2000): Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med, 28 pp. 3581–3587

233. Hornig B, Landmesser U, Kohler C, Ahlersmann D, Spiekermann S, Christoph A, Tatge H, Drexler H(2001): Comparative effect of ACE inhibition and angiotensin type 1 receptor antagonism on bioavailability of nitric oxide in patients with coronary artery disease: role of superoxide dismutase. Circulation. 103: 799–805.

234. Horwich TB, et al. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 2003;108(7):833–8.

235. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acutekidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10: R73.

236. Hoste EA, De Waele JJ, Gevaert SA, Uchino S, Kellum JA. Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis. Nephrol Dial Transplant 2010; 25: 747–58.

237. Hostetter TH. Hyperfiltration and glomerulosclerosis. Semin Nephrol 2003; 23: 194–199.

238. Howard P.A., M.I. Dunn. ggressive diuresis for severe heart failure in the elderly. Chest, 119 (2001), pp. 807–810

239. Howard, AD, Moore, J Jr, Gouge, SF et al. Routine serologic tests in the differential diagnosis of the adult nephrotic syndrome. Am J Kidney Dis. 1990; 15: 24–30

240. Howie-Esquivel J., M. White. Biomarkers in acute cardiovascular disease. J Cardiovasc Nurs, 23 (2008), pp. 124–131

241. Hruska KA, Mathew S, Lund RJ et al. The pathogenesis of vascular calcification in the chronic kidney disease mineral bone disorder: the links between bone and the vasculature. Semin Nephrol 2009; 29: 156–165.

242. Huang CH, et al. Diagnostic accuracy of tissue Doppler echocardiography for patients with acute heart failure. Heart 2006;92(12):1790–4. 755

243. Hunt SA, Abraham WT, Chin MH et al. (2005). "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult"

244. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46(6):e1–82.

245. Hunter JG, Boon NA, Davidson S, Colledge NR, Walker B (2006). Davidson's principles & practice of medicine. Elsevier/Churchill Livingstone. p. 544. ISBN 0-443-10057-8.

246. Ichimura T., C.C. Hung, S.A. Yang, J.L. Stevens, J.V. Bonventre. Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. Am J Physiol Renal Physiol, 286 (2004), pp. F552–F563

247. Inglis SC, et al. Extending the horizon in chronic heart failure: effects of multidisciplinary, home-based intervention relative to usual care. Circulation 2006;114(23):2466–73.

248. Ishwaran H, Takahara G: Independent and identically distributed Monte Carlo algorithms for semiparametric linear mixed models. J Am Stat Assoc 2002, 97:1154-1166.

249. Iyengar S, Abraham WT. Diuretics for the treatment of acute decompensated heart failure. Heart Fail Rev 2007;12(2):125–30.

250. Izuhara Y, Nangaku M, Takizawa S et al. A novel class of advanced glycation inhibitors ameliorates renal and cardiovascular damage in experimental rat models. Nephrol Dial Transplant 2008; 23: 497–509.

251. Jackson C: Multi-State Models for Panel Data: The msm Package for R. J Stat Softw 2011, 38:1-29.

252. Jacqmin-Gadda H, Sibillot S, Proust C, Molina JM, Thiebaut R: Robustness of the linear mixed model to misspecified error distribution. Comput Stat Data Anal 2007, 51:5142-5154.

253. Jafar TH, Stark PC, Schmid CH et al. The effect of angiotensin-converting-enzyme inhibitors on progression of advanced polycystic kidney disease. Kidney Int 2005; 67: 265–271.

254. Jessup M, Abraham WT, Casey DE et al. (April 2009). "2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation". Circulation 119 (14): 1977–2016. doi:10.1161/CIRCULATIONAHA.109.192064. PMID 19324967.

255. Jessup M. Aldosterone blockade and heart failure. N Engl J Med, 348 (2003), pp. 1380–1382

256. Jie K.E., M.C. Verhaar, M.J. Cramer, et al. Erythropoietin and the cardiorenal syndrome: Cellular mechanisms on the cardiorenal connectors. Am J Physiol Renal Physiol, 291 (2006), pp. F932–F944

257. Jie KE, Verhaar MC, Cramer MJ, van der Putten K, Gaillard CA, Doevendans PA, Koomans HA, Joles JA, Braam B. Erythropoietin and the cardiorenal syndrome: cellular mechanisms on the cardiorenal connectors. Am J Physiol Renal Physiol. 2006; 291: F932–F944.

258. Johnson D.W., A.M. Craven, N.M. Isbel. Modification of cardiovascular risk in hemodialysis patients: an evidence-based review. Hemodial Int, 11 (2007), pp. 1–14

259. Joly P, Commenges D, Helmer C, Letenneur L: A penalized likelihood approach for an illness-death model with interval-censored data: application to age-specific incidence of dementia. Biostatistics 2002, 3:433-443.

260. Jones BL, Nagin DS: Advances in group-based trajectory modeling and an SAS procedure for estimating them. Sociol Methods Res 2007, 35:542-571.

261. Josep., H. Skali, N. Anavekar, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction, J Am Soc Nephrol, 17 (2006), pp. 2886–2891

262. Juenger J, Schellberg D, Kraemer S et al. (March 2002). "Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables". Heart 87 (3): 235–41. doi:10.1136/heart.87.3.235. PMC 1767036. PMID 11847161.

263. Jung T, Wickrama KAS: An introduction to latent class growth analysis and growth mixture modeling. Soc Personal Psychol Compass 2008, 2:302-317.

264. Juurlink D.N., M.M. Mamdani, D.S. Lee, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med, 351 (2004), pp. 543–551

265. Juurlink D.N., M.M. Mamdani, et al. Appropriateness of spironolactone prescribing in heart failure patients: a population-based study. J Card Fail, 12 (2006), pp. 205–210

266. Kasiske BL, O′Donnell MP, Schmitz PG et al. Renal injury of diet-induced hypercholesterolemia in rats. Kidney Int 1990; 37: 880–891.

267. Kazory A, Ross EA. Anemia: the point of convergence or divergence for kidney disease and heart failure? J Am Coll Cardiol. 2009;53:639–647.

268. Keane WF. The role of lipids in renal disease: future challenges. Kidney Int Suppl 2000; 75: S27–S31.

269. Keith D.S., G.A. Nichols, C.M. Gullion, J.B. Brown, D.H. Smith. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med, 164 (2004), pp. 659–663

270. Kelly K.J. Distant effects of experimental renal ischemia/reperfusion injury. J Am Soc Nephrol, 14 (2003), pp. 1549–1558

271. Keltai M, Tonelli M, Mann JF, Sitkei E, Lewis BS, Hawken S, et al. Renal function and outcomes in acute coronary syndrome: impact of clopidogrel. Eur J Cardiovasc Prev Rehabil. 2007;14:312–318.

272. Keltai M., M. Tonelli, J.F. Mann, et al. Renal function and outcomes in acute coronary syndrome: Impact of clopidogrel. Eur J Cardiovasc Prev Rehabil, 14 (2007), pp. 312–318

273. Kim JS: Maximum likelihood estimation for the proportional hazards model with partly interval-censored data. J R Stat Soc Ser B (Stat Methodol) 2003, 65:489-502.

274. Kinugawa S, Tsutsui H, Hayashidani S, Ide T, Suematsu N, Satoh S, Utsumi H, Takeshita A. Treatment with dimethylthiourea prevents left ventricular remodeling and failure after experimental myocardial infarction in mice: role of oxidative stress. Circ Res. 2000; 87: 392–398.

275. Knight E.L., R.J. Glynn, K.M. McIntyre, H. Mogun, J. Avorn. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the Studies Of Left Ventricular Dysfunction (SOLVD). Am Heart J, 138 (1999), pp. 849–855

276. Kobayashi, M., Hirawa, N., & Morita, S. (2010). Silent brain infarction and rapid decline of kidney function in patients with CKD: a prospective cohort study. American Journal of Kidney Diseases, 56(3):468-476.

277. Koelling TM, et al. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation 2005;111(2):179–85.

278. Kohan DE, Pritchett Y, Molitch M et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. J Am Soc Nephrol 2011; 22: 763–772.

279. Kohl M, Heinze G: PSHREG: A SAS® macro for proportional and nonproportional substribution hazards regression with competing risk data. In Technical report 08/2012, Center for Medical Statistics, Informatics and Intelligent Systems. Medical University of Vienna; 2012.

280. Kohli, HS, Bhat, A, Aravindan et al. Spectrum of renal failure in elderly patients. Int Urol Nephrol. 2006; 38: 759–765 (Epub 2007 Jan 23.)

281. Konstam MA, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. Jama 2007;297(12):1319–31.

282. Konstam MA, Gheorghiade M, Burnett JC Jr., Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007; 297: 1319–1331.

283. Kotecha, Dipak; Holmes, Jane; Krum, Henry; Altman, Douglas G; Manzano, Luis; Cleland, John G F; Lip, Gregory Y H; Coats, Andrew J S; Andersson, Bert; Kirchhof, Paulus; von Lueder, Thomas G; Wedel, Hans; Rosano, Giuseppe; Shibata, Marcelo C; Rigby, Alan; Flather, Marcus D (December 2014). "Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis". The Lancet 384 (9961): 2235–2243. doi:10.1016/S0140-6736(14)61373-8. PMID 25193873.

284. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant 2009; 24: 1232–1237.

285. Kozak LJ, Owings MF, Hall MJ. National Hospital Discharge Survey: 2002 annual summary with detailed diagnosis and procedure data. Vital Health Stat 13, 2005;(158):1–199.

286. Krishnagopalan S., A. Kumar, J.E. Parrillo, A. Kumar. Myocardial dysfunction in the patient with sepsis. Curr Opin Crit Care, 8 (2002), pp. 376–388

287. Krug AW, Grossmann C, Schuster C et al. (October 2003). "Aldosterone stimulates epidermal growth factor receptor expression". J. Biol. Chem. 278 (44): 43060–6. doi:10.1074/jbc.M308134200. PMID 12939263.

288. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009; 373: 1275–1281.

289. Krumholz HM, Chen YT, Wang Y, Vaccarino V, Radford MJ, Horwitz RI (2000). "Predictors of readmission among elderly survivors of admission with heart failure". Am. Heart J. 139 (1 Pt 1): 72–7. doi:10.1016/S0002-8703(00)90311-9. PMID 10618565.

290. Kumar, B. Paladugu, J. Mensing, A. Kumar, J.E. Parrillo. Nitric oxide-dependent and -independent mechanisms are involved in TNF-alpha-induced depression of cardiac myocyte contractility. Am J Physiol Regul Integr Comp Physiol, 292 (2007), pp. R1900–R1906

291. Kunz R, Wolbers M, Glass T et al. The COOPERATE trial: a letter of concern. Lancet 2008; 371: 1575–1576.

292. Laederach K, Weidmann P. Plasma and urinary catecholamines as related to renal function in man. Kidney Int. 1987; 31: 107–111.

293. Langenberg C, Bagshaw S, May CN, Bellomo R. The histopathologyof septic acute kidney injury: a systematic review. Crit Care 2008; 12: R38.

294. Lassnigg, E.R. Schmid, M. Hiesmayr, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? Crit Care Med, 36 (2008), pp. 1129–1137

295. Latini R., S. Masson, I. Anand, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. Eur Heart J, 25 (2004), pp. 292–299

296. Law CG, Brookmeyer R: Effects of mid-point imputation on the analysis of doubly censored data. Stat Med 1992, 11:1569-1578.

297. Lee W, Campoy S, Smits G et al. Effectiveness of a chronic kidney disease clinic in achieving K/DOQI guideline targets at initiation of dialysis--a single-centre experience. Nephrol Dial Transplant 2007; 22: 833–838.

298. Leelahavanichkul A, Yuen PS, Star RA. Animal models of sepsis and sepsis-induced kidney injury. J Clin Invest 2009; 119: 2868–78.

299. Leffondre K, Touraine C, Helmer C, Joly P: Interval-censored time-to-event and competing risk with death: is the illness-death model more accurate than the Cox model? Int J Epidemiol 2013, 42:1177-1186.

300. Leier CV. Positive inotropic therapy: an update and new agents. Curr Probl Cardiol 1996; 21(8):521–81.

301. Lele, S., Shah, S., McCullough, P., & Rajapurkar, M. (2009). Serum catalytic iron as a novel biomarker of vascular injury in acute coronary syndromes. EuroIntervention, 5(3):336-342.

302. Lemley KV, Boothroyd DB, Blouch KL, Nelson RG, Jones LI, Olshen RA, Myers BD: Modeling GFR trajectories in diabetic nephropathy. Am J Physiol - Renal 2005, 289:F863-F870.

303. Levey AS, Coresh J: Chronic kidney disease. Lancet 2012, 379:165-180.

304. Levey, AS, Bosch, JP, Lewis, JB, Greene, T, Rogers, N, Roth, D, and Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med. 1999; 130: 461–470

305. Levin A, Djurdjev O, Beaulieu M et al. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. Am J Kidney Dis 2008; 52: 661–671.

306. Levin A, Lewis M, Mortiboy P et al. Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. Am J Kidney Dis 1997; 29: 533–540.

307. Levin, C.R. Thompson, J. Ethier, et al. Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. Am J Kidney Dis, 34 (1999), pp. 125–134

308. Levin, R.N. Foley. Cardiovascular disease in chronic renal insufficiency. Am J Kidney Dis, 36 (2000), pp. S24–S30

309. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345: 851–860.

310. Lewis J, Salem MM, Chertow GM, et al. Atrial natriuretic factor in oliguric acute renal failure. Am J Kidney Dis 2000; 36: 767–74.

311. Liang F., J. O'Rear, U. Schellenberger, et al. Evidence for functional heterogeneity of circulating B-type natriuretic peptide. J Am Coll Cardiol, 49 (2007), pp. 1071–1078

312. Liang K.V., A.W. Williams, E.L. Greene, M.M. Redfield. Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med, 36 (2008), pp. S75–S88

313. Liang, X., Liu, S., Chen, Y., & et al. (2010). Combination of urinary kidney injury molecule-1 and interleukin-18 as early biomarker for the diagnosis and progressive assessment of acute kidney injury following cardiopulmonary bypass surgery: a prospective nested casecontrol study. Biomarkers, 15(4):332-339.

314. Liangos, M.C. Perianayagam, V.S. Vaidya, et al. Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol, 18 (2007), pp. 904–912

315. Lim HJ, Zhang X, Dyck R, Osgood N: Methods of Competing Risks Analysis of End-Stage Renal Disease and Mortality among People with Diabetes. BMC Med Res Methodol 2010, 10:97.

316. Lim SW, Choi BS et al. Inhibitory effect of pravastatin on transforming growth factor beta1-inducible gene h3 expression in a rat model of chronic cyclosporine nephropathy. Am J Nephrol 2005; 25: 611–620.

317. Lin J, Bonventre JV. Prevention of radiocontrast nephropathy. Curr Opin Nehrol Hypertens 2005; 14: 105–10.

318. Liss, P, Persson, PB, Hansell, P, and Lagerqvist, B. Renal failure in 57 925 patients undergoing coronary procedures using iso-osmolar or low-osmolar contrast media. Kidney Int. 2006 Nov; 70: 1811–1817 (Epub 2006 Sep 27.)

319. Little WC, Zile MR, Kitzman DW et al. The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure. J Card Fail 2005; 11: 191–195.

320. Liu YL, Prowle J, Licari E, Uchino S, Bellomo R. Changes in blood pressure before the development of nosocomial acute kidney injury. Nephrol Dial Transplant 2009; 24: 504–11.

321. Liu, Feng; Chen, Yanmei; Feng, Xuguang; Teng, Zhonghua; Yuan, Ye; Bin, Jianping; Hosoda, Toru (5 March 2014). "Effects of Beta-Blockers on Heart Failure with Preserved Ejection Fraction: A Meta-Analysis". PLoS ONE 9 (3): e90555. doi:10.1371/journal.pone.0090555. PMID 24599093.

322. Liuzzo, L.M. Biasucci, J.R. Gallimore, et al. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med, 331 (1994), pp. 417–424

323. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS Trial) Am J Cardiol. 1992;70:479–487.

324. **Logar C.M., C.A. Herzog, S.** Beddhu. Diagnosis and therapy of coronary artery disease in renal failure, end-stage renal disease, and renal transplant populations. Am J Med Sci, 325 (2003), pp. 214–227

325. Lopez B, et al. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. J Am Coll Cardiol 2004; 43(11):2028–35.

326. Loria V., I. Dato, F. Graziani, L.M. Biasucci. Myeloperoxidase: a new biomarker of inflammation in ischemic heart disease and acute coronary syndromes. Mediators Inflamm, 2008 (2008), p. 135625

327. Loscalzo, Joseph; Fauci, Anthony S.; Braunwald, Eugene; Dennis L. Kasper; Hauser, Stephen L; Longo, Dan L. (2008). Harrison's Principles of Internal Medicine (17 ed.). McGraw-Hill Medical. p. 1447.ISBN 978-0-07-147693-5.

328. Loutzenhiser R, Griffi n K, Williamson G, Bidani A. Renal autoregulation: new perspectives regarding the protective and regulatory roles of the underlying mechanisms. Am J Physiol Regul Integr Comp Physiol 2006;

290: R1153–67. 44 Oliver JA, Verna EC. Aff erent mechanisms of sodium retention in cirrhosis and hepatorenal syndrome. Kidney Int 2010; 77: 669–80.

329. Macedo E, Malhotra R, Claure-Del Granado R, Fedullo P, Mehta RL. Defi ning urine output criterion for acute kidney injury in critically ill patients. Nephrol Dial Transplant 2011; 26: 509–15.

330. Macedo E, Mehta RL. Prerenal failure: from old concepts to new paradigms. Curr Opin Crit Care 2009; 15: 467–73.

331. Maeder MT, Holst DP, Kaye DM. Tricuspid regurgitation contributes to renal dysfunction in patients with heart failure. J Card Fail. 2008; 10: 824–830.

332. Magil AB. Interstitial foam cells and oxidized lipoprotein in human glomerular disease. Mod Pathol 1999; 12: 33–40.

333. Mahajan A, Simoni J, Sheather SJ et al. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int 2010; 78: 303–309.

334. Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. Rev Cardiovasc Med 2002;(3 Suppl 4):S10–7.

335. Maisel AS, Katz N, Hillege HL, and the Acute Dialysis Quality Initiative consensus group. Biomarkers in kidney and heart disease. Nephrol Dial Transplant 2011; 26: 62–74.

336. Maisel, J.E. Hollander, D. Guss, et al. Primary results of the rapid emergency department heart failure outpatient trial (REDHOT): A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. J Am Coll Cardiol, 44 (2004), pp. 1328–1333

337. Malbrain ML, Cheatham ML, Kirkpatrick, Sugrue M, Parr M, De Waele J, Balogh Z, Leppäniemi A, Olvera C, Ivatury R, D'Amours S, Wendon J, Hillman K, Johansson K, Kolkman K, Wilmer A. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. Intensive Care Med. 2006; 32: 1722–1732.

338. Mann DL, Chakinala M (2012). Harrison's principles of internal medicine: Chapter 234. Heart Failure and Cor Pulmonale. (18th ed.). New York: McGraw-Hill. ISBN 978-0071748896.

339. Mann JF, Green D, Jamerson K et al. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol 2010; 21: 527–535.

340. Mann T, et al. Effect of nitroprusside on regional myocardial blood flow in coronary artery disease. Results in 25 patients and comparison with nitroglycerin. Circulation 1978;57(4):732–8.

341. Masuda M, Yamada T, Okuyama Y, et al. Sodium bicarbonate improves long-term clinical outcomes compared with sodium chloride in patients with chronic kidney disease undergoing an emergent coronary procedure. Circ J 2008; 72: 1610–14.

342. Mavric Z, et al. Usefulness of blood lactate as a predictor of shock development in acute myocardial infarction. Am J Cardiol 1991;67(7):565–8.

343. McAlister F.A., J. Ezekowitz, M. Tonelli, P.W. Armstrong. Renal insufficiency and heart failure: Prognostic and therapeutic implications from a prospective cohort study. Circulation, 109 (2004), pp. 1004–1009

344. McAlister FA, Ezekowtiz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation. 2003; 109: 1004–1009.

345. McClellen W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, Tse TF, Wasserman B, Leiserowitz M. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin. 2004; 20: 1501–1510.

346. McCulloch CE, Lin H, Slate EH, Turnbull BW: Discovering subpopulation structure with latent class mixed models. Stat Med 2002, 21:417-429.

347. McCullough P.A. Contrast induced nephropathy. J Am Coll Cardiol, 51 (2008), pp. 1419–1428.

348. McCullough P.A., K.R. Sandberg. Chronic kidney disease and sudden death: strategies for prevention. Blood Purif, 22 (2004), pp. 136–142

349. McDonagh, Theresa A. (2011). Oxford textbook of heart failure. Oxford: Oxford University Press. p. 3. ISBN 9780199577729.

350. McMurray JJ, Pfeffer MA (2005). "Heart failure". Lancet 365 (9474): 1877–89. doi:10.1016/S0140-6736(05)66621-4. PMID 15924986.

351. McMurray, M., Trivax, J., & McCullough, P. (2009). Serum cystatin C, renal filtration function, and left ventricular remodeling. Circulation. Heart Failure, 2(2):86-89.

352. Mebazaa, M. Gheorghiade, I.L. Pina, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes Crit Care Med, 36 (2008), pp. S129–S139

353. Mehdi UF, Adams-Huet B, Raskin P et al. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol 2009; 20: 2641–2650.

354. Mehra MR, Kobashigawa J, Starling R et al. (September 2006). "Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates–2006". J. Heart Lung Transplant. 25 (9): 1024–42. doi:10.1016/j.healun.2006.06.008. PMID 16962464.

355. Mehta RL, Kellum JA, Shah SV, and the Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31.

356. Melamed ML, Astor B, Michos ED et al. 25-hydroxyvitamin D levels, race, and the progression of kidney disease. J Am Soc Nephrol 2009; 20: 2631–2639.

357. Meldrum DR, Moore FA, Moore EE, Franciose RJ, Sauaia A, Burch JM. Prospective characterization and selective management of the abdominal compartment syndrome. Am J Surg. 1997; 45: 667–673.

358. Meyer T.W., T.H. Hostetter. Uremia. N Engl J Med, 357 (2007), pp. 1316–1325

359. Meyer, M. Huelsmann, P. Wexberg, et al. N-terminal pro-B-type natriuretic peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. Crit Care Med, 35 (2007), pp. 2268–2273

360. Michiels B, Molenberghs G, Bijnens L, Vangeneugden T, Thijs H: Selection models and pattern-mixture models to analyse longitudinal quality of life data subject to drop-out. Stat Med 2002, 21:1023-1041.

361. Mishra J., C. Dent, R. Tarabishi, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet, 365 (2005), pp. 1231–1238.

362. Misra M, Vonesh E, Churchill DN, Moore HL, Van Stone JC, Nolph KD: Preservation of glomerular filtration rate on dialysis when adjusted for patient dropout. Kidney Int 2000, 57:691-696.

363. Moe GW, et al. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007;115(24):3103–10.

364. Mohanram A, Zhang Z, Shahinfar S, Keane WF, Brenner BM, Toto RD. Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. Kidney Int. 2004; 66: 1131–1138.

365. Moorhead JF, Chan MK, El-Nahas M et al. Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet 1982; 2: 1309–1311.

366. Moreau R, Lebrec D. Acute kidney injury: new concepts. Nephron Physiol 2008; 109: 73–79.

367. Mori K., K. Nakao. Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. Kidney Int, 71 (2007), pp. 967–970.

368. Mori, K., & Nakao, K. (2007). Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. Kidney International, 71:967-970.

369. Muirhead N. Update in nephrology. Ann Intern Med 2010; 152: 721–25.

370. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009; 53: 589–596.

371. Muthen B, Shedden K: Finite mixture modeling with mixture outcomes using the EM algorithm. Biometrics 1999, 55:463-469.

372. Nakamura T, Fukui M, Ebihara I et al. Low protein diet blunts the rise in glomerular gene expression in focal glomerulosclerosis. Kidney Int 1994; 45: 1593–1605.

373. Nakao N, Yoshimura A, Morita H et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet 2003; 361: 117–124.

374. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. J Clin Invest 1985; 76: 667–675.

375. National Institute for Health and Clinical Excellence. Clinical guideline 108: Chronic heart failure - Management of chronic heart failure in adults in primary and secondary care . London, August 2010.

376. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis, 39 (2002), pp. S1–S266

377. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002, 39:S1-266.

378. Navaneethan SD, Nigwekar SU, Sehgal AR et al. Aldosterone antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev 2009: CD007004.

379. Needham D.M., K.A. Shufelt, G. Tomlinson, J.W. Scholey, G.E. Newton. Troponin I and T levels in renal failure patients without acute coronary syndrome: a systematic review of the literature. Can J Cardiol, 20 (2004), pp. 1212–1218

380. Nephrol Dial Transplant, 23 (2008), pp. 1203–1210

381. Neubauer S (2007). "The failing heart – an engine out of fuel". N Engl J Med 356 (11): 1140–51. doi:10.1056/NEJMra063052. PMID 17360992.

382. Neuhofer W., D. Pittrow. Role of endothelin and endothelin receptor antagonists in renal disease. Eur J Clin Invest, 36 (Suppl 3)(2006), pp. 78–88

383. Nguyen H.B., T. Losey, J. Rasmussen, et al. Interrater reliability of cardiac output measurements by transcutaneous Doppler ultrasound: Implications for noninvasive hemodynamic monitoring in the ED. Am J Emerg Med, 24 (2006), pp. 828–835

384. Nguyen M.T., G.F. Ross, C.L. Dent, P. Devarajan. Early prediction of acute renal injury using urinary proteomics. Am J Nephrol, 25 (2005), pp. 318–326.

385. Nieminen MS, Böhm M, Cowie MR et al. (February 2005). "Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology". Eur. Heart J. 26 (4): 384–416. doi:10.1093/eurheartj/ehi044. PMID 15681577.

386. Nieminen MS, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26(4):384–416.

387. Nishida Y, Oda H, Yorioka N. Effect of lipoproteins on mesangial cell proliferation. Kidney Int Suppl 1999; 71: S51–S53.

388. Nishiyama A, Abe Y. Molecular mechanisms and therapeutic strategies of chronic renal injury: renoprotective effects of aldosterone blockade. J Pharmacol Sci 2006; 100: 9–16.

389. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol. 2008; 51: 1268–1274.

390. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ: When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant 2013, 28:2670-2677.

391. Nowbar, AN; Mielewczik, M; Karavassilis, M; Dehbi, HM; Shun-Shin, MJ; Jones, S; Howard, JP; Cole, GD; Francis, DP; DAMASCENE writing, group (Apr 28, 2014). "Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis.". BMJ (Clinical research ed.) 348: g2688. doi:10.1136/bmj.g2688. PMC 4002982. PMID 24778175.

392. O'Hare AM, Batten A, Burrows NR, Pavkov ME, Taylor L, Gupta I, Todd-Stenberg J, Maynard C, Rodriguez RA, Murtagh FE, Larson EB, Williams DE: Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. Am J Kidney Dis 2012, 59:513-522.

393. Obermayr RP, Temml C, Gutjahr G et al. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008; 19: 2407–2413.

394. Odell PM, Anderson KM, D'Agostino RB: Maximum likelihood estimation for interval-censored data using a Weibull-based accelerated failure time model. Biometrics 1992, 48:951-959.

395. Ogden LG; Bazzano LA; Vupputuri S et al. (2001). "Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study". Arch. Intern. Med. 161 (7): 996–1002. doi:10.1001/archinte.161.7.996. PMID 11295963.

396. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol. 2008;51:103–112.

397. Opdam H.I., L. Wan, R. Bellomo. A pilot assessment of the FloTrac cardiac output monitoring system. Intensive Care Med, 33 (2007), pp. 344–349

398. Ortega R, Gines P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology 2002; 36: 941–48.

399. Ota T, Takamura T, Ando H et al. Preventive effect of cerivastatin on diabetic nephropathy through suppression of glomerular macrophage recruitment in a rat model. Diabetologia 2003; 46: 843–851.

400. Packer M, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334(21):1349–55.

401. Packer M, Miller AB. Canphysicians always explain the results of clinical trials? Acasestudy of amlodipine in heart failure. Am J Cardiol 1999;84(4A):1L–2L.

402. Pagani FD, et al. Extracorporeal life support to left ventricular assist device bridge to heart transplant: A strategy to optimize survival and resource utilization. Circulation 1999; 100(19 Suppl):II206–10.

403. Palazzuoli, D.S. Silverberg, F. Iovine, et al. Effects of beta-erythropoietin treatment on left ventricular remodeling, systolic function, and B-type natriuretic peptide levels in patients with the cardiorenal anemia syndrome. Am Heart J, 154 (2007), p. 645 e9–15

404. Palmer SC, Hayen A, Macaskill P et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. Jama 305: 1119–1127.

405. Panichi V., U. Maggiore, D. Taccola, et al. Interleukin-6 is a stronger predictor of total and cardiovascular mortality than C-reactive protein in haemodialysis patients. Nephrol Dial Transplant, 19 (2004), pp. 1154–1160

406. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrol Dial Transplant. 1996; 11: 1277–1285.

407. **Parikh C.R., A. Jani, J. Mishra, et al.** Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. Am J Transplant, 6 (2006), pp. 1639–1645.

408. Parikh S.V., J.A. de Lemos. Biomarkers in cardiovascular disease: integrating pathophysiology into clinical practice. Am J Med Sci, 332 (2006), pp. 186–197

409. Parving HH, Brenner BM, McMurray JJ et al. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. Nephrol Dial Transplant 2009; 24: 1663–1671.

410. Patel A, MacMahon S, Chalmers J et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560–2572.

411. Peacock WF. Using the emergency department clinical decision unit for acute decompensated heart failure. Cardiol Clin 2005;23(4):569–88, viii.

412. Pépin, MN, Bouchard, J, Legault, L, and Éthier, J. Diagnostic performance of fractional excretion of urea and fractional excretion of sodium in the evaluations of patients with acute kidney injury with or without diuretic treatment. Am J Kidney Dis. 2007; 50: 566–573

413. Peraira-Moral J. Roberto, Núñez-Gil Ivan J. (19 January 2012). "Anaemia in heart failure: intravenous iron therapy". E-journal of the ESC Council for Cardiology Practice 10 (16).

414. Perazella, MA. Drug-induced renal failure: update on new medications and unique mechanisms of nephrotoxicity. Am J Med Sci. 2003; 325: 349–362

415. Pergola PE, Raskin P, Toto RD et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med 2011; 365: 327–336.

416. Pfeffer MA, Burdmann EA, Chen CY et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009; 361: 2019–2032.

417. Pfuntner A., Wier L.M., Stocks C. Most Frequent Conditions in U.S. Hospitals, 2011. HCUP Statistical Brief #162. September 2013. Agency for Healthcare Research and Quality, Rockville, MD. [1]

418. Phisitkul S, Khanna A, Simoni J et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. Kidney Int 2010; 77: 617–623.

419. Pintilie M: Competing risks: A Practical Perspective. Chichester, England: John Wiley & Sons, Ltd; 2006.

420. Pitt B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348(14):1309–21.

421. Pitt B, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341(10):709–17.

422. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309–1321.

423. Pitt, F. Zannad, W.J. Remme, Randomized Aldactone Evaluation Study Investigators, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med, 341 (1999), pp. 709–717

424. Platell C, Hall J, Dobb G. Impaired renal function due to raised intraabdominal pressure. Intensive Care Med 1990; 16: 328–29.

425. Ponda MP, Hostetter TH. Aldosterone antagonism in chronic kidney disease. Clin J Am Soc Nephrol 2006; 1: 668–677.

426. Proust-Lima C, Sene M, Taylor JM, Jacqmin-Gadda H: Joint latent class models for longitudinal and time-to-event data: A review. Stat Methods Med Res 2014, 23:74-90.

427. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol 2010; 6: 107–15.

428. Prowle JR, Ishikawa K, May CN, Bellomo R. Renal blood flow during acute renal failure in man. Blood Purif 2009; 28: 216–25.

429. Prowle JR, Molan MP, Hornsey E, Bellomo R. Cine phase-contrast magnetic resonance imaging for the measurement of renal blood flow. Contrib Nephrol 2010; 165: 329–36.

430. Putter H, Fiocco M, Geskus RB: Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007, 26:2389-2430.

431. RamachandraRao SP, Zhu Y, Ravasi T et al. Pirfenidone is renoprotective in diabetic kidney disease. J Am Soc Nephrol 2009; 20: 1765–1775.

432. Ramadan F.H., N. Masoodi, A.A. El-Solh. Clinical factors associated with hyperkalemia in patients with congestive heart failure. J Clin Pharm Ther, 30 (2005), pp. 233–239

433. Ramchandra R, Wan L, Hood SG, Frithiof R, Bellomo R, May CN. Septic shock induces distinct changes in sympathetic nerve activity to the heart and kidney in conscious sheep. Am J Physiol Regul Integr Comp Physiol 2009; 297: R1247–53.

434. Raphael C, Briscoe C, Davies J et al. (2007). "Limitations of the New York Heart Association functional classification system and self□reported walking distances in chronic heart failure". Heart 93 (4): 476–82. doi: 10.1136/hrt.2006.089656. PMC 1861501. PMID 17005715.

435. Rattazzi M., M. Puato, E. Faggin, B. Bertipaglia, F. Grego, P. Pauletto New markers of accelerated atherosclerosis in end-stage renal disease J Nephrol, 16 (2003), pp. 11–20

436. Ravid M, Brosh D, Ravid-Safran D et al. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. Arch Intern Med 1998; 158: 998–1004.

437. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. J Clin Invest 2006; 116: 288–296.

438. Richards N, Harris K, Whitfield M et al. Primary care-based disease management of chronic kidney disease (CKD), based on estimated glomerular filtration rate (eGFR) reporting, improves patient outcomes. Nephrol Dial Transplant 2008; 23: 549–555.

439. Riksen N.P., D.J. Hausenloy, D.M. Yellon. Erythropoietin: ready for prime-time cardioprotection. Trends Pharmacol Sci, 29 (2008), pp. 258–267

440. Rizopoulos D: JM: An R package for the joint modelling of longitudinal and time-to-event data. J Stat Softw 2010, 35:1-33.

441. Robins JM, Rotnitzky A, Zhao LP: Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. J Am Stat Assoc 1995, 90:106-121.

442. Rodriguez M, Lorenzo V. Parathyroid hormone, a uremic toxin. Semin Dial 2009; 22: 363–368.

443. Roghi, S. Savonitto, C. Cavallini, et al. Impact of acute renal failure following percutaneous coronary intervention on long-term mortality. J Cardiovasc Med, 9 (2008), pp. 375–381.

444. Ronco C, Bellomo R, Homel P, et al. Eff ect of diff erent doses in continuous veno-venous haemofi ltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000; 356: 26–30.

445. **Ronco C., Z. Ricci, A. Brendolan, R. Bellomo, F. Bedogni.** Ultrafiltration in patients with hypervolemia and congestive heart failure. Blood Purif, 22 (2004), pp. 150–163

446. Ronco. NGAL: an emerging biomarker of acute kidney injury. Int J Artif Organs, 31 (2008), pp. 199–200.

447. Rosamond W, Flegal K, Furie K et al. (January 2008). "Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee". Circulation 117 (4): e25–146. doi:10.1161/CIRCULATIONAHA.107.187998.

448. Rosansky SJ: Renal function trajectory is more important than chronic kidney disease stage for managing patients with chronic kidney disease. Am J Nephrol 2012, 36:1-10.

449. Rosenberg P, Yancy CW. Noninvasive assessment of hemodynamics: an emphasison bioimpedance cardiography.CurrOpin Cardiol2000;15(3):151–5.

450. Rovin BH, Tan LC. LDL stimulates mesangial fibronectin production and chemoattractant expression. Kidney Int 1993; 43: 218–225.

451. Roy P., J. Bouchard, R. Amyot, F. Madore. Prescription patterns of pharmacological agents for left ventricular systolic dysfunction among hemodialysis patients. Am J Kidney Dis, 48 (2006), pp. 645–651

452. Ruggenenti P., A. Perna, G. Remuzzi, Gruppo Italiano di Studi Epidemiologici in Nefrologia. ACE inhibitors to prevent end-stage renal disease: when to start and why possibly never to stop: a post hoc analysis of the REIN trial results: Ramipril Efficacy In Nephropathy. J Am Soc Nephrol, 12 (2001), pp. 2832–2837

453. Ruiz-Ortega M, Ruperez M, Lorenzo O, Esteban V, Blanco J, Mezzano S, Egido J. Angiotensin II regulates the synthesis of proinflammatory cytokines and chemokines in the kidney. Kidney Int. 2002; 82: S12–S22.

454. Rule, AD, Rodeheffer, RJ, Larson, TS et al. Limitations of estimating glomerular filtration rate from serum creatinine in the general population. Mayo Clin Proc. 2006; 81: 1427–1434

455. Ruster C, Wolf G. Renin-angiotensin-aldosterone system and progression of renal disease. J Am Soc Nephrol 2006; 17: 2985–2991.

456. Sackner-Bernstein J, Aaronson KD. Nesiritide for acute decompensated heart failure: does the benefit justify the risk? Curr Cardiol Rep 2007;9(3):187–93

457. Sackner-Bernstein J.D., H.A. Skopicki, K.D. Aaronson. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation, 111 (2005), pp. 1487–1491

458. Sagi SV, Mittal S, Kasturi KS, Sood GK. Terlipressin therapy for reversal of type 1 hepatorenal syndrome: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2010; 25: 880–85.

459. Sakata Y., T. Masuyama, K. Yamamoto, et al. Calcineurin inhibitor attenuates left ventricular hypertrophy, leading to prevention of heart failure in hypertensive rats. Circulation, 102 (2000), pp. 2269–2275

460. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007; 56: 1310–18.

461. Sandhu S, Wiebe N, Fried LF et al. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol 2006; 17: 2006–2016.

462. Sandhu, S, Wiebe, N, Fried, LF, and Tonelli, M. Statins for Improving renal outcomes: a meta-analysis. J Am Soc Nephrol. 2006 Jul; 17: 2006–2016 (Epub 2006 Jun 8.)

463. Saotome T, Ishikawa K, May CN, Birchall IE, Bellomo R. The impact of experimental hypoperfusion on subsequent kidney function. Intensive Care Med 2010; 36: 533–40.

464. Sarnak M.J., B.E. Coronado, T. Greene, et al. Cardiovascular disease risk factors in chronic renal insufficiency. Clin Nephrol, 57 (2002), pp. 327–335

465. Schaeffner ES, Kurth T, Curhan GC et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol 2003; 14: 2084–2091.

466. Schindler R., W. Beck, R. Deppisch, et al. Short bacterial DNA fragments: Detection in dialysate and induction of cytokines. J Am Soc Nephrol, 15 (2004), pp. 3207–3214

467. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. N Engl J Med. 2009; 361: 932–934.

468. Schluchter MD, Greene T, Beck GJ: Analysis of change in the presence of informative censoring: application to a longitudinal clinical trial of progressive renal disease. Stat Med 2001, 20:989-1007.

469. Schluchter MD: Conditional mixed models adjusting for non-ignorable drop-out with administrative censoring in longitudinal studies. Stat Med 2004, 23:3489-3503.

470. Schoolwerth AC, Sandler RS, Hoffman PM et al. Effects of nephron reduction and dietary protein content on renal ammoniagenesis in the rat. Kidney Int 1975; 7: 397–404.

471. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med 2004; 351: 159–69.

472. Scolari F, Ravani P, Gaggi R, Santostefano M, Rollino C, Stabellini N, Colla L, Viola BF, Maiorca P, Venturelli C, Bonardelli S, Faggiano P, Barrett BJ: The challenge of diagnosing atheroembolic renal disease: clinical features and prognostic factors. Circulation 2007, 116:298-304.

473. Sculpher MJ, et al. Low doses vs. high doses of the angiotensin converting-enzyme inhibitor lisinopril in chronic heart failure: a cost-effectiveness analysis based on the Assessment of Treatment with Lisinopril and Survival (ATLAS) study.The ATLAS Study Group.Eur J HeartFail 2000;2(4):447–54.

474. Selby N.M., C.W. McIntyre. The acute cardiac effects of dialysis. Semin Dial, 20 (2007), pp. 220–228

475. ***Shale*** SN, Abramowitz M, Hostetter TH et al. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis 2009; 54: 270–277.

476. Sharma K, Ix JH, Mathew AV et al. Pirfenidone for diabetic nephropathy. J Am Soc Nephrol 2011; 22: 1144–1151.

477. Shigeyama J, Yasumura Y, Sakamoto A et al. (December 2005). "Increased gene expression of collagen Types I and III is inhibited by beta-receptor blockade in patients with dilated cardiomyopathy". Eur. Heart J. 26 (24): 2698–705. doi:10.1093/eurheartj/ehi492. PMID 16204268.

478. Shimizu T, Fukagawa M, Kuroda T et al. Pirfenidone prevents collagen accumulation in the remnant kidney in rats with partial nephrectomy. Kidney International Supplement 1997; 63: S239–S243.

479. Shlipak MG. Pharmacotherapy for heart failure in patients with renal insufficiency. Ann Intern Med. 2003;138:917–924.

480. Silva RP, Barbosa PH, Kimura OS, Sobrinho CR, Sousa Neto JD, Silva FA, et al. Prevalance of anemia and its association with cardio-renal syndrome. Int J Cardiol. 2007;120:232–236.

481. Silverberg D.S., D. Wexler, M. Blum, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol, 35 (2000), pp. 1737–1744

482. Silverberg DS, Wexler D, Iaina A, Steinbruch S, Wollman Y, Schwartz D. Anemia, chronic renal disease and congestive heart failure--the cardio renal anemia syndrome: the need for cooperation between cardiologists and nephrologists. Int Urol Nephrol. 2006;38:295–310.

483. Simon E, Martin D, Buerkert J. Contribution of individual superficial nephron segments to ammonium handling in chronic metabolic acidosis in the rat. Evidence for ammonia disequilibrium in the renal cortex. J Clin Invest 1985; 76: 855–864.

484. Simpson DP. Control of hydrogen ion homeostasis and renal acidosis. Medicine (Baltimore) 1971; 50: 503–541.

485. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, for the CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006; 355: 2085–2098.

486. Siu YP, Leung KT, Tong MK et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006; 47: 51–59.

487. Snyder JJ, Collins AJ. Association of preventive health care with atherosclerotic heart disease and mortality in CKD. J Am Soc Nephrol 2009; 20: 1614–1622.

488. Sommerer, J. Beimler, V. Schwenger, et al. Cardiac biomarkers and survival in haemodialysis patients. Eur J Clin Invest, 37 (2007), pp. 350–356

489. **Sorensen C.R., B. Brendorp, C. Rask-Madsen, L. Kober, E. Kjoller, C.** Torp-Pedersen. The prognostic importance of creatinine clearance after acute myocardial infarction. Eur Heart J, 23 (2002), pp. 948–952

490. Sowers JR, Whaley-Connell A, Epstein M. Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. Ann Intern Med 2009; 150: 776–783.

491. Spanaus K.S., F. Kronenberg, E. Ritz, et al. B-type natriuretic peptide concentrations predict the progression of nondiabetic chronic kidney disease: the mild-to-moderate kidney disease study. Clin Chem, 53 (2007), pp. 1264–1272

492. Sporn MB, Liby KT, Yore MM et al. New synthetic triterpenoids: potent agents for prevention and treatment of tissue injury caused by inflammatory and oxidative stress. J Nat Prod 2011; 74: 537–545.

493. Srisawat N, Wen X, Lee M, et al. Urinary biomarkers predict renal recovery in critically ill patients. Clin J Am Soc Nephrol 2011; published online July 14. DOI:10.2215/CJN.11261210.

494. St John Sutton M, Pfeffer MA, Moye L, Plappert T, Rouleau JL, Lamas G, Rouleau J, Parker JO, Arnold MO, Sussex B, Braunwald E. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. Circulation. 1997; 96: 3294–3299.

495. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. Am J Kidney Dis 2003; 41: 310–318.

496. Stel VS, Dekker FW, Tripepi G, Zoccali C, Jager KJ: Survival analysis II: Cox regression. Nephron Clin Pract 2011, 119:c255-260.

497. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemody-namics in chronic heart failure. Jama 1989;261(6):884–8.754

498. Stevenson LW. Are hemodynamic goals viable in tailoring heart failure therapy? Hemodynamic goals are relevant. Circulation 2006;113(7):1020–7, discussion 1033.

499. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ (June 2002). "The current cost of heart failure to the National Health Service in the UK". Eur. J. Heart Fail. 4 (3): 361–71. doi:10.1016/S1388-9842(01)00198-2. PMID 12034163.

500. Stirban A, Negrean M, Stratmann B et al. Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. Diabetes Care 2006; 29: 2064–2071.

501. Stoegeman CA, Kallenberg CGM. Pathogenesis of angiitis. In: Davison AM, ed. Oxford textbook of clinical nephrology. Oxford: Oxford University Press, 2005: 741–52.

502. Strömberg A, Mårtensson J. (Apr 2003). "Gender differences in patients with heart failure". Eur. J. Cardiovasc. Nurs. 2 (1): 7–18. doi:10.1016/S1474-5151(03)00002-1. PMID 14622644.

503. Suki W.N., R. Zabaneh, J.L. Cangiano, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int, 72 (2007), pp. 1130–1137

504. Sun W.Y., I.W. Reiser, S.Y. Chou. Risk factors for acute renal insufficiency induced by diuretics in patients with congestive heart failure. Am J Kidney Dis, 47 (2006), pp. 798–808

505. Supavekin S., W. Zhang, R. Kucherlapati, F.J. Kaskel, L.C. Moore, P. Devarajan. Differential gene expression following early renal ischemia/reperfusion. Kidney Int, 63 (2003), pp. 1714–1724

506. Suresh M., K. Farrington. Natriuretic peptides and the dialysis patient. Semin Dial, 18 (2005), pp. 409–419

507. Tangri N, Weiner DE. Uric acid, CKD, and cardiovascular disease: confounders, culprits, and circles. Am J Kidney Dis 56: 247–250.

508. Tanji N, Markowitz GS, Fu C et al. Expression of advanced glycation end products and their cellular receptor RAGE in diabetic nephropathy and nondiabetic renal disease. J Am Soc Nephrol 2000; 11: 1656–1666.

509. Taylor, RS; Sagar, VA; Davies, EJ; Briscoe, S; Coats, AJ; Dalal, H; Lough, F; Rees, K; Singh, S (Apr 27, 2014). "Exercise-based rehabilitation for heart failure.". The Cochrane database of systematic reviews 4: CD003331. doi:10.1002/14651858.CD003331.pub4. PMID 24771460.

510. Taylor, RS; Sagar, VA; Davies, EJ; Briscoe, S; Coats, AJ; Dalal, H; Lough, F; Rees, K; Singh, S (27 April 2014). "Exercise-based rehabilitation for heart failure". The Cochrane database of systematic reviews 4: CD003331. doi:10.1002/14651858.CD003331.pub4. PMID 24771460.

511. Tessone, S. Gottlieb, I.M. Barbash, et al. Underuse of standard care and outcome of patients with acute myocardial infarction and chronic renal insufficiency. Cardiology, 108 (2007), pp. 193–199

512. Throssell D, Harris KP, Bevington A et al. Renal effects of metabolic acidosis in the normal rat. Nephron 1996; 73: 450–455.

513. Titan SM, Zatz R, Graciolli FG et al. FGF-23 as a predictor of renal outcome in diabetic nephropathy. Clin J Am Soc Nephrol 2011; 6: 241–247.

514. Tojo A, Onozato ML, Kobayashi N, Goto A, Matsuoka H, Fujita T. Angiotensin II and oxidative stress in Dahl salt-sensitive rat with heart failure. Hypertension. 2002; 40: 834–839.

515. Tokmakova M.P., H. Skali, S. Kenchaiah, et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the survival and ventricular enlargement (SAVE) study. Circulation, 110 (2004), pp. 3667–3673

516. Tokuyama H., D.J. Kelly, Y. Zhang, R.M. Gow, R.E. Gilbert. Macrophage infiltration and cellular proliferation in the non-ischemic kidney and heart following prolonged unilateral renal ischemia. Nephron Physiol, 106 (2007), pp. 54–62

517. **Hostetter TH**, Tolins JP, Hostetter MK,. Hypokalemic nephropathy in the rat. Role of ammonia in chronic tubular injury. J Clin Invest 1987; 79: 1447–1458.

518. Tonelli M, Curhan G, Pfeffer M et al. Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. Circulation 2009; 120: 1784–1792.

519. Tonelli M., N. Wiebe, B. Culleton, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol, 17 (2006), pp. 2034–2047

520. Topic Review – Heart Failure By Osama Gusbi, MD. Albany Medical Review – January 2002

521. Torio CM, Andrews RM. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011. HCUP Statistical Brief #160. Agency for Healthcare Research and Quality, Rockville, MD. August 2013. [3]

522. Torres VE, Cowley Jr BD, Branden MG et al. Long-term ammonium chloride or sodium bicarbonate treatment in two models of polycystic kidney disease. Exp Nephrol 2001; 9: 171–180.

523. Touraine C, Gerds TA, Joly P: The SmoothHazard package for R: Fitting regression models to interval-censored observations of illness-death models. In Research report 13/12. University of Copenhagen: Department of Biostatistics; 2013.

524. Traynor, J, Mactier, R, Geddes, CC, and Fox, JG. How to measure renal function in clinical practice. BMJ. 2006; 333: 733–737

525. Tripepi G, Jager KJ, Dekker FW, Zoccali C: Linear and logistic regression analysis. Kidney Int 2008, 73:806-810.

526. Tsutsui H, Matsushima S, Kinugawa S et al. (May 2007). "Angiotensin II type 1 receptor blocker attenuates myocardial remodeling and preserves diastolic function in diabetic heart". Hypertens. Res. 30 (5): 439–49. doi:10.1291/hypres.30.439. PMID 17587756.

527. Uchino S, Bellomo R, Kellum JA, and the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators Writing Committee. Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. Int J Artif Organs 2007; 30: 281–92.

528. Uchino S, Bellomo R, Morimatsu H, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. Crit Care Med 2009; 37: 2576–82.

529. Uchino S., R. Bellomo, D. Goldsmith, S. Bates, C. Ronco. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med, 34 (2006), pp. 1913–1917

530. Upadhyay A, Earley A, Haynes SM et al. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med 2011; 154: 541–548.

531. **Urqhuart B.L., A.A.** House. Assessing plasma total homocysteine in patients with end-stage renal disease. Perit Dial Int, 27 (2007), pp. 476–488

532. Vaidya V.S., V. Ramirez, T. Ichimura, N.A. Bobadilla, J.V. Bonventre. Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury. Am J Physiol Renal Physiol, 290 (2006), pp. F517–F529

533. Van der Meer P, Lok DJ, Januzzi JL, de la Porte PW, Lipsic E, van Wijngaarden J, et al. Adequacy of endogenous erythropoietin levels and mortality in anaemic heart failure patients. Eur Heart J. 2008;29:1510–1515.

534. Van der Velde M, Matsushita K, Coresh J et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 2011; 79: 1341–1352.

535. Van Slyke DD, Linder GC, Hiller A et al. The excretion of ammonia and titratable acid in nephritis. J Clin Invest 1926; 2: 255–288.

536. VandeVoorde R.G., T.I. Katlman, Q. Ma, et al. Serum NGAL and cystatin C as predictive biomarkers for acute kidney injury. J Am Soc Nephrol, 17 (2006), p. 404A

537. Vaziri ND, Dicus M, Ho ND, Boroujerdi-Rad L, Sindhu RK. Oxidative stress and dysregulation of superoxide dismutase and NADPH oxidase in renal insufficiency. Kidney Int. 2003; 63: 179–185.

538. Veinot J.P., G.A. Wells, A.A. House. Increased mortality in hemodialyzed patients with elevated serum troponin T: a one-year outcome study. Clin Biochem, 32 (1999), pp. 647–652

539. Verbeke G, Molenberghs G: Linear mixed models for longitudinal data. New York: Springer; 2009.

540. Verma, S.D. Solomon. Optimizing care of heart failure after acute MI with an aldosterone receptor antagonist. Curr Heart Fail Rep, 4 (2007), pp. 183–189

541. Vesey DA, Cheung C, Pat B, Endre Z, Gobé G, Johnson DW. Erythropoietin protects against ischaemic acute renal injury. Nephrol Dial Transplant. 2004; 19: 348–355.

542. Vogt L, Waanders F, Boomsma F et al. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. J Am Soc Nephrol 2008; 19: 999–1007.

543. von Lueder, TG; Atar, D; Krum, H (Oct 2013). "Diuretic use in heart failure and outcomes.". Clinical pharmacology and therapeutics 94 (4): 490–8. doi:10.1038/clpt.2013.140. PMID 23852396.

544. Vonesh EF, Greene T, Schluchter MD: Shared parameter models for the joint analysis of longitudinal data and event times. Stat Med 2006, 25:143-163.

545. Wagener G., M. Jan, M. Kim, et al. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology, 105 (2006), pp. 485–491.

546. Wagener, HP and Keith, NM. Diffuse arteriolar disease with hypertension and the associated retinal lesions. Medicine. 1939; 18: 317–430

547. Wali RK, Wang GS, Gottlieb SS, Bellumkonda L, Hansalia R, Ramos E, Drachenberg C, Papadimitriou J, Brisco MA, Blahut S, Fink JC, Fisher ML, Bartlett St, Weir MR. Effect of kidney transplantation on left ventricular systolic function and congestive heart failure in patients with end-stage renal disease. J Am Coll Cardiol. 2005; 451051–1060.

548. Walker JE, Giri SN, Margolin SB. A double-blind, randomized, controlled study of oral pirfenidone for treatment of secondary progressive multiple sclerosis. Mult Scler 2005; 11: 149–158.

549. Wan L., T. Naka, S. Uchino, R. Bellomo. A pilot study of pulse contour cardiac output monitoring in patients with septic shock. Crit Care Resusc, 7 (2005), p. 165

550. Wang CS, et al. Does this dyspneic patient in the emergency department have congestive heart failure? Jama 2005;294(15):1944–56.

551. Wang X, Greene T: Nonparametric multistate representations of survival and longitudinal data with measurement error. Stat Med 2012, 31:2303-2317.

552. Ward, JF, Kaplan, GW, Mevorach, R, Stock, JA, and Cilento, BG Jr. Refined microscopic urinalysis for red blood cell morphology in the evaluation of asymptomatic microscopic hematuria in a pediatric population. J Urol. 1998; 160: 1492–1495

553. Wei LJ, Lin DY, Weissfeld L: Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Stat Assoc 1989, 84:1065-1073.

554. Wei SY, Chang YY, Mau LW et al. Chronic kidney disease care program improves quality of pre-end-stage renal disease care and reduces medical costs. Nephrology (Carlton) 2010; 15: 108–115.

555. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J. 1999; 138: 285–290.

556. Wellwood, J., Ellis, B., Price, R., Hammond, K., Thompson, A., & Jones, N. (1975). Urinary N-acetyl- beta-D-glucosaminidase activities in patients with renal disease. British Medical Journal, 3(5980):408-411.

557. Wen CP, David Cheng TY, Chan HT et al. Is high serum uric acid a risk marker or a target for treatment? Examination of its independent effect in a large cohort with low cardiovascular risk. Am J Kidney Dis 56: 273–288.

558. Wesson DE, Simoni J, Broglio K et al. Acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. Am J Physiol Renal Physiol 2011; 300: F830–F837.

559. Wilkinson-Berka JL, Kelly DJ, Koerner SM et al. ALT-946 and aminoguanidine, inhibitors of advanced glycation, improve severe nephropathy in the diabetic transgenic (mREN-2)27 rat. Diabetes 2002; 51: 3283–3289.

560. Williams ME, Bolton WK, Khalifah RG et al. Effects of pyridoxamine in combined phase 2 studies of patients with type 1 and type 2 diabetes and overt nephropathy. Am J Nephrol 2007; 27: 605–614.

561. Winton FR. The influence of venous pressure on the isolated mammalian kidney. J Physiol. 1931; 72: 49–61.

562. Witteles R.M., D. Kao, D. Christopherson, et al. Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction a randomized, double-blind, placebo-controlled clinical trial. J Am Coll Cardiol, 50 (2007), pp. 1835–1840

563. Wolf M. Forging forward with 10 burning questions on FGF23 in kidney disease. J Am Soc Nephrol 2010; 21: 1427–1435.

564. Wolf SC, Brehm BR, Gaschler F et al. Protective effects of endothelin antagonists in chronic renal failure. Nephrol Dial Transplant 1999; 14(Suppl 4): 29–30.

565. Wong F, Nadim MK, Kellum JA, et al. Working party proposal for a revised classifi cation system of renal dysfunction in patients with cirrhosis. Gut 2011; 60: 702–09.

566. Woods LL. Mechanisms of renal hemodynamic regulation in response to protein feeding. Kidney Int 1993; 44: 659–675.

567. Wright R.S., G.S. Reeder, C.A. Herzog, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. Ann Intern Med, 137 (2002), pp. 563–570

568. Wysokinski, WE, Gosk-Bierska, I, Greene, EL, Grill, D, Wiste, H, and McBane, RD II. Clinical characteristics and long-term follow-up of patients with renal vein thrombosis. Am J Kidney Dis. 2008; 51: 224–232

569. Xu S., P. Venge. Lipocalins as biochemical markers of disease. Biochim Biophys Acta, 1482 (2000), pp. 298–307.

570. Yancy CW, et al. Safety and feasibility of using serial infusions of nesiritide for heart failure in an outpatient setting (from the FUSION I trial). Am J Cardiol 2004;94(5):595–601.

571. Yancy CW, et al. The Second Follow-up Serial Infusions of Nesiritide (FUSION II) trial for advanced heart failure: study rationale and design. Am Heart J 2007;153(4):478–84.

572. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE et al. (2013). "2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". Circulation 128 (16): e240–e327. doi:10.1161/CIR.0b013e31829e8776. PMID 23741058.

573. Yeoh HH, Tiquia HS, Abcar AC et al. Impact of predialysis care on clinical outcomes. Hemodial Int 2003; 7: 338–341.

574. Yorgun H., A. Deniz, K. Aytemir. Cardiogenic shock secondary to combination of diltiazem and sotalol. Intern Med J, 38 (2008), pp. 221–222.

575. **Young JB, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, O'Connor CM, She L, Sun JL, Yancy CW, Fonarow GC,** for the OPTIMIZE-HF Investigators and Coordinators. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). Am J Cardiol. 2008; 101: 223–230.

576. **Zandi-Nejad K, Brenner BM.** Strategies to retard the progression of chronic kidney disease. Med Clin North Am 2005; 89: 489–509.

577. Zappitelli M., K.K. Washburn, A.A. Arikan, et al. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. Crit Care, 11 (2007), p. R84

578. **Zatz R, Anderson S, Meyer TW et al.** Lowering of arterial blood pressure limits glomerular sclerosis in rats with renal ablation and in experimental diabetes. Kidney Int Suppl 1987; 20: S123–S129.

579. **Zhang W, Liu M, Wu Y et al.** Protective effects of atorvastatin on chronic allograft nephropathy in rats. J Surg Res 2007; 143: 428–436.

580. **Zhang Y, Kong J, Deb DK et al.** Vitamin D receptor attenuates renal fibrosis by suppressing the renin-angiotensin system. J Am Soc Nephrol 21: 966–973.

581. **Zoja C, Morigi M, Remuzzi G.** Proteinuria and phenotypic change of proximal tubular cells. J Am Soc Nephrol 2003; 14(Suppl 1): S36–S41.

الهدف من الرسالة:

1- دراسة معدل انتشار متلازمة القلب والكلى بمستشفيات بنها الجامعية.

2- دراسة معدل انتشار كل نوع من متلازمة القلب والكلى.

3- دراسة معدل انتشار كل نوع من متلازمة القلب والكلى فى الأقسام المختلفة بالمستشفى.

4- دراسة معدل انتشار أسباب كل نوع.

5- دراسة تأثير متلازمة القلب والكلى على معد الوفيات.

طرق الدراسة والبحث:

تم اجراء هذه الدراسة على 250 مريض فى مستشفيات بنها الجامعية من الأقسام المختلفة.

كانت مجموعة البحث تخضع لهذه الشروط.

1- مرضى فشل عضلة القلب الحاد المصاحب بفشل كلوى حاد.

2- مرضى فشل عضلة القلب الحاد المزمن المصاحب بفشل كلوى مزمن.

3- مرضى الفشل الكلوى الحاد والمصاحب بفشل حاد فى عضلة القلب.

4- مرضى الفشل الكلوى المزمن المصاحب بفشل مزمن فى عضلة القلب.

5- الأمراض النظامية التى تؤثر على القلب والكلى.

المستثنى من البحث:

1- المرضى أقل من 20 عام.

2- مرضى الفشل الكلوى الحاد المزمن دون مرضى القلب.

الفحصوات التى تم اجراءها:-

1- نسبة البولينا والكرياتين.

2- تحليل بول.

3- صورة دم كاملة.

4- نسبة صوديوم وبوتاسيوم بالدم.

5- غازات بالدم.

6- تحليل سكر صائم وفاطر.

7- اشعة تليفزيونية على البطن.

8- اشعة تليفزيونية على القلب.

9- رسم قلب.

نتائج البحث:

- **كان معدل انتشار متلازمة القلب والكلى أعلى فى الذكور من الاناث.**
- **وكان معدل الوفيات أعلى فى النوع الأول والخامس من متلازمة القلب والكلى.**
- **أدت متلازمة القلب والكلى إلى زيادة مدة الاقامة بالمستشفى فى جميع الأنواع.**
- **كانت اسباب الوفاة فى النوع الأول ناتجة عن ذبحة صدرية مصاحبة بفشل كلوى حاد أما فى النوع الخامس كانت نتيجة للذئبة الحمراء وتخثر الدم.**

المقدمه

تعرف متلازمة القلب والكلى بأنها إختلال نسيجى سريري يتميز بأن أى إختلال فى وظيفة كل من القلب أو الكلى يؤدى إلى تغيرات وظيفية فى العضو الآخر.

تنقسم متلازمة القلب والكلى إلى خمسة اقسام حسب تقسيم رونكو:

القسم الاول: وتسمى متلازمة القلب والكلى الحادة بحيث أن الفشل الحاد فى عضلة القلب يؤدى إلى قصور كلوى حاد.

القسم الثاني: وتسمى متلازمة القلب والكلى المزمنة بحيث أن فشل عضلة القلب المزمن يؤدى إلى قصور كلوى مزمن.

القسم الثالث: وتسمى متلازمة الكلى والقلب الحادة ويحدث فيها قصور كلوى حاد يؤدى إلى إختلال حاد فى وظيفة القلب مثل اضطراب ضربات القلب أو فشل فى عضلة القلب.

القسم الرابع: وتسمى متلازمة الكلى والقلب المزمنه ويحدث فيها قصور كلوى مزمن يؤدى إلى اضطراب فى وظيفة القلب.

القسم الخامس: وتسمى متلازمة القلب والكلى الثانوية ويحدث فيها اختلال فى وظيفة القلب والكلى نتيجة لمرض جهازى مثل مرض تعفن الدم أو الذئبة الحمراء.

تستقبل الكلى ٢٠% من إنتاج القلب الدموى لذلك تعمل الكلى والقلب بصورة مترابطه بحيث أن أى تغيرات فى حجم وضغط الدم فى الأذين يؤدى إلى فعل منعكس يغير من وظيفة الكلى بمنعى أن زيادة الضغط الأذينى يؤدى إلى تثبيط افراز **أنتي ديوريتك هرمون** وهرمون أرجينين فاذوبريسين (هنرى جاور) وهذا الفعل المنعكس يتم عن طريق العصب الحائر ولذلك فأن قطع هذا العصب يزيل هذا الفعل المنعكس كما أن هذا الفعل المنعكس مسئول عن زيادة كمية البول بعد سرعة ضربات القلب الأذينية الطارئة.

لا حظ ديبولد وجود حبيبات فى الأذين وعندما تم حقن هذه الحبيبات فى الفئران أدت إلى زيادة ملحوظه فى كمية الصوديوم والماء بالبول كما وجد أن هذه الحبيبات تحتوى على هرمون يسمى الببتيد الأذينى المدر للصوديوم والذى يؤدى إلى تثبيط جهاز الرينين أنجيوتنسين الدوستيرون والجهاز السمبثاوى مما يؤدى إلى توسع شرايين الكلى والجسم كله. يحتوى البطين على مادة مماثلة تسمى ببتيد المخ المدر للصوديوم حيث أنه تم إكتشافه فى المخ للمرة الأولى.

أكثر من ٣٠% من حالات فشل عضلة القلب الحاد يؤدى إلى اختلال فى وظيفة الكلى.

أن أمراض القلب منتشرة فى حالات القصور الكلوى المزمن حيث أن ٤٣,٦% من حالات الوفاة لمرضى القصور الكلوى المزمن ناتجة عن اضطراب في وظيفة القلب.

القسم الأول من متلازمة القلب والكلى يحدث به قصور كلوى حاد بصورة اكثر خطورة مع نقص وظيفة البطين الأيسر وتصل النسبة إلى ذروتها فى حالات الصدمات القلبية.

إن معدل انتشار اضطرابات القلب فى مرضى الفشل الكلوى المزمن تصل إلى ٢٥%.

القسم الثالث ويسمى متلازمة الكلى والقلب الحادة يحدث به قصور كلوى حاد يؤدى إلى زيادة معدلات البوتاسيوم فى الدم مما يؤدى إلى اضطراب فى ضربات القلب وحتى إلى توقف عضلة القلب كذلك عدم علاج حمضية الدم تؤدى إلى تثبيط عضلة القلب.

القسم الخامس والمسمى بمتلازمة القلب والكلى الثانوية يعتبر مرض تعفن الدم هو الأكثر خطورة فى تاثيره على القلب والكلى.

تؤدى جلطات القلب الحادة إلى نقص كمية الدم الذى يضخ من القلب مما يؤدى إلى قلة كمية الدم الواردة للدورة الدموية الكلوية ينتج عن ذلك زيادة المقاومة فى شرايين الكلى مما ينشط جهاز الرينين أنجيوتنسين الدوستيرون والجهاز السمبثاوى حتى يحافظ على ضغط الدم الشريانى لكن هذا يؤدى إلى نقص الدم الوارد إلى الشريان الكلوى ومعدل الفلترة الكبيبية مما يؤدى إلى قصور كلوى حاد.

معدل انتشار متلازمة القلب والكلى في مستشفيات بنها الجامعية

رسالة

مقدمة توطئة للحصول على درجة الماجستير في أمراض الباطنة

مقدمة من الطبيب/ عمرو احمد محمود إبراهيم

بكالوريوس الطب والجراحة

تحت اشراف

ا0د/ محمد يحي صديق

أستاذ أمراض الباطنة - طب بنها

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استاذ ورئيس قسم امراض الباطنة - طب بنها

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مدرس امراض الباطنة - طب بنها

كلية الطب جامعة بنها

2015