Cardiovascular diseases (CVD) incur a heavy burden of morbidity and mortality among patients with chronic kidney disease (CKD), particularly among the elderly. It is estimated that about 22-25% of all adults beyond the age of 65 years have moderate or severe renal dysfunction.\(^1,2\)

Traditional risk factors such as hypertension, hypertriglyceridemia, low HDL levels and physical inactivity have a stronger association with cardiovascular mortality; however this association is weaker with risk factors such as high CRP, fibrinogen, interleukin 6 (IL-6), factor VIIIc and lipoprotein(a) which are novel for patients with CKD.\(^3\)

The risk of CVD among patients with CKD starts in the earlier stages of CKD and with time becomes progressively worse with worsening renal insufficiency. Aging itself is associated with progressive decline in glomerular filtration rate: 0.75ml decline per year.\(^3\) Aging is also a risk for development of cardiovascular diseases\(^3\) both related to atherosclerosis and age related structural changes in the myocardium, such as left ventricular hypertrophy.\(^2,4\)

Thus, when cardiac arrhythmia presents among the elderly CKD/end stage renal disease (ESRD) patients, it is likely to carry a very high risk of mortality and morbidity. In the present review we present the available data on the epidemiology, pathogenesis, and treatment strategies which are derived from published studies, US Renal Data System (USRDS) and treatment guidelines published by the National Kidney Foundation.

**Structural changes**

Normal aging process is characterized by histopathological changes that are conducive to the development of atrial fibrillation. With aging there is fat deposition in the atrioventricular node, interatrial septum and the right atrium which leads to hypertrophic and sclerotic changes.\(^5\) Ultimately the myocardial fibers are replaced by collagen along with diffuse fatty deposits and connective tissue infiltration. This provides the necessary substrate for reentrant tachyarrhythmias; disparate conduction velocities, unidirectional block and reentry. Atrial fibrosis is frequently seen among patients with prolonged episodes of atrial fibrillation. Hence, an incremental increase in the prevalence of atrial fibrillation is noted with advancing age. Increase in cardiac interstitial cell volume which is a finding specific for uremia is usually seen among the elderly patients with CKD. Interstitial fibrosis may promote electrical instability by producing reentrant ventricular tachycardia and ventricular fibrillation.\(^6\) Heterogeneity in repolarization as reflected by prolonged QT dispersion (the difference in the longest and shortest QT intervals on a surface lead EKG) is associated with an increased incidence of ventricular arrhythmias and sudden cardiac death. Post dialysis patients have prolonged QT dispersion.\(^7,8\)

In an unselected patient population undergoing either hemodialysis or peritoneal dialysis, corrected QT dispersion was associated with increased total mortality and a trend towards increased arrhythmic mortality.\(^9\)

**Autonomic imbalance**

Among older patients with ESRD on hemodialysis, significant abnormalities of heart rate variability suggestive of autonomic dysfunction was noted.\(^10\) Plasma norepinephrine level was noted to be higher among patients with ESRD on hemodialysis and was an independent predictor of cardiovascular mortality, perhaps due to arrhythmias such as ventricular tachycardia and ventricular fibrillation.\(^11\) The rate of sympathetic nervous discharge was significantly higher among patients with ESRD on hemodialysis.\(^12\)

**Electrolyte imbalance**

Hyperphosphatemia promotes vascular calcification by worsening secondary hyperparathyroidism as well as direct deposition of calcium phosphate in the arterial wall.\(^13\) Metastatic calcium deposits in the conduction system among patients with chronic renal failure also have been reported to cause atrio-ventricular block.\(^14\) Electrolyte perturbations are frequently seen among patients with CKD as well as ESRD patients: conditions which are conducive to the development
of ventricular tachycardia and ventricular fibrillation. From the USRDS analysis, cardiac arrest occurred most frequently on Mondays and Tuesdays—the days of dialysis when the oscillation in the hemodynamics and perturbations in electrolytes homeostasis are at their peaks.

**Malnutrition, inflammation and atherosclerosis**

Atherosclerotic heart disease is more prevalent among patients with ESRD than in the general population. The increase in CVD among ESRD patients is not limited to traditional risk factors. It is proposed that non-traditional risks such as pro-inflammatory states, oxidative stresses may be responsible in accelerated atherosclerosis leading to ischemic heart diseases. Some of the markers of inflammation are high cytokines: interleukin 6, tissue necrosis factor-α and high C reactive protein level.  

**Left ventricular hypertrophy, congestive heart failure and coronary artery disease**

Left ventricular hypertrophy is an independent risk for sudden cardiac death and ventricular arrhythmia among patients with ESRD.  

Additionally cardiomyopathy promotes progressive decline in left ventricular ejection fraction leading to prohibitively increased risks of arrhythmic deaths.  

Among patients with ESRD on dialysis the prevalence for coronary artery disease, left ventricular hypertrophy, and congestive heart failure are 40%, 75% and 40% respectively. The annual mortality from cardiovascular diseases is estimated at 9% even after corrected for age, race and presence of diabetes mellitus. This risk is 10 to 20 times higher than in patients without ESRD.

**Arrhythmic syndromes**

**Atrial fibrillation**

Atrial fibrillation is the most common sustained arrhythmia among humans. About 2.2 million Americans have atrial fibrillation. The prevalence increases directly with age: 3-5% of people over the age of 65 have atrial fibrillation whereas approximately 10% of all people over the age of 80 have atrial fibrillation.

About 15% of all patients with stroke have documented atrial fibrillation. Atrial fibrillation is more common among hypertensive patients and patients with congestive heart failure. Due to its associated co-morbidities such as stroke, atrial fibrillation should be dealt with in distinction from other "arrhythmias".  

As ESRD is commonly associated with hypertension, left ventricular hypertrophy and congestive heart failure it is thought that ESRD patients have an increased prevalence of atrial fibrillation, although no population based studies are available in this high risk group. The increased risk factors for atrial fibrillation among dialysis patients are due to age, cardiac dilatation, and abnormal calcium phosphorous homeostasis.

Among hospitalized ESRD patients for atrial fibrillation the leading cause of death was cardiac arrest of unknown cause (19%), cardiac arrest due to cardiac arrhythmia (8%), of unknown causes (26%), acute myocardial infarction (7%), cardiomyopathy (3%), and stroke (3%). This USRDS based study also noted that the baseline use of coumadin and higher systolic blood pressure were associated with lower risk of mortality. Older age was confirmed to be the highest risk for hospitalized atrial fibrillation among ESRD patients. (p=0.0002 HR9.96, 95% CI 2.98-33.28).

**Sudden cardiac death**

USRDS database is a government mandated database for all renal failure patients in the United States which collects data from two sources: ICD 9 CM codes and from Death Notification Forms. In the USRDS database, cardiovascular diseases account for 45% of all causes of mortality. Cardiac arrest and arrhythmia accounted for 61% of all cardiac deaths among dialysis patients: among those who survive an episode of cardiac arrest one year survival is abysmally low at 17% among those without diabetes mellitus, and 13% among those with diabetes mellitus. The rate of cardiac arrest among prevalent dialysis patients has dropped from 75 per 1000 patient-years in 1994 to 62 per 1000 patient-years. Among the general Medicare population the cardiac arrest rate in CKD patients has fallen from 24 per 1000 patient-years to 17 per 1000 patient-years over the same period. Inpatient one-year mortality rate from sudden cardiac arrest has changed little in over a decade: 36/1000 in 1991 to 37/1000 in 2002. Similarly, outpatient mortality rate from cardiac arrest has remained unchanged: it was 58/1000 in 1991 and remains the same in 2002. The greatest decline in mortality was observed among patients with non-sudden cardiac deaths: the rate dropped from 115 per 1000 patient-years in 1991 to 92 in 2002. This is presumably due to better usage of beta blockers, statins and angiotensin converting enzyme inhibitors. Perhaps the outcome can be improved further by implementing measures to prevent arrhythmic death such as availability of automatic external defibrillator (AED's) and implantation of ICD's.  

After initiation of hemodialysis among ESRD patients, the event rate of cardiac arrest increases in the first month and stabilizes by six months and remains constant over the next 30 months. However among peritoneal dialysis patients, the rate of cardiac arrest remains stable for six months then the rate increases slowly thereafter. At the end of three years the event-free probability is 70% in both modalities of dialysis.  

In the 1999-2000 cohorts of patients only 6.5% of hemodialysis patients underwent coronary revascularization in the three years after the initiation of the dialysis. Among the elderly patients only 6% had the procedure 2 years prior to initiation and 14% in the three years following. The utilization of implantable cardioverter defibrillator is woefully inadequate with only 3.4% patients receiving the device.  

Proportion of elderly patient contributing to the pool of dialysis recipients who suffer cardiac arrest has increased during the period 1991-2002.  

USRDS is a government sponsored administrative database which collects data on each patient who starts dialysis.
Although the data base is quite comprehensive, it lacks in specificity in defining the mechanism of arrhythmic deaths. The data collection form does not contain specific information whether the patient died from tachyarrhythmias such as VT or VF or brady arrhythmias such as advanced degrees of heart block or asystole secondary to pump failure. This has therapeutic implications as treatment may be entirely different for this group of patients. Despite its inadequacies, USRDS remains the only large database where an attempt has been made for collection of accurate data.

In a cohort of 77,000 dialyzed patients the incidence of cardiac arrest (CA) was 7 per 100,000 hemodialysis sessions. The highest risks associated with CA was the type of dialysate used, advanced age and presence of diabetes mellitus. Sixty percent of the patients succumbed to a recurrent episode within 48 hours of the initial episode.

In an earlier study abnormal ambulatory electrocardiogram, which included patients with second degree or greater AV block or by Lown grade 3 or greater ventricular ectopy, was associated with normal survival if coronary artery disease was absent versus 90% if abnormal ECG. Additionally, in the presence of CAD, six months survival was 83% with a normal ECG, whereas it was 54% with an abnormal 24-hour ECG.

Among patients with ESRD on peritoneal dialysis ventricular arrhythmias were noted in up to 43% of patients on two 24-hour ambulatory electrocardiography recordings and were only noted among patients with left ventricular hypertrophy. Ventricular arrhythmias were seen in 57% of the patients. The overwhelming majority of these patients had left ventricular hypertrophy.

Implantable cardioverter and defibrillators

Most primary prevention and secondary prevention implantable cardioverter defibrillator (ICD) trials excluded patients who had end stage renal disease. A recent study has reported only 30% usage of ICD in the general population among patients who have survived cardiac arrest and have class I indication for implantation of ICD's. In the USRDS based study of ESRD patients, the usage of ICD's was abysmally low at 7% among a select group of patients with CA one month after discharge from the hospital. The overall reduction in the risk of death was 42% in patients who received ICD's which is comparable to the risk reduction of 38% among patients in the AVID trial.

In a retrospective study of ICD patients we observed that total survival was adversely affected by the presence of CKD (Fig. 1); Arrhythmic deaths were higher with worsening renal failure (Fig. 2); Usage of cardio-protective medications was lower; Patients with CKD required higher energy (defibrillation threshold or DFT's) to defibrillate them (Fig. 3). This relationship was incremental i.e. DFT's were progressively higher with worsening renal failure. This raises an important but disturbing concern: Could it be that some of these arrhythmic deaths were due to ineffective defibrillation. Prospective studies are needed to confirm the finding of these observations.

Guidelines for Management

The National Kidney Foundation through its K/DOQI committee has recently published a 138 page guidelines for treating patients with cardiovascular disease who are on dialysis. The full recommendations are beyond the scope of this review. The salient features of the recommendations are:
1. Management of CVD, specifically ischemic heart disease should be similar to the general population. All patients should be assessed for cardiovascular diseases at the beginning of dialysis.

2. A baseline electrocardiogram should be done at the beginning of dialysis and should be repeated every year.

3. A baseline echocardiogram should be done once dry weight has been achieved and should be repeated every three years.

4. Automatic screening stress test is not recommended among dialysis patients.

5. If symptoms or high risk status do warrant stress testing it must include an imaging modality such as nuclear scanning or stress echocardiography.

6. Among patients who have change in symptoms (recurrent hypotension, CHF not responding to therapy) and baseline LV dysfunction with LVEF <40% should undergo evaluation for CAD.

7. Patients waiting for renal transplant should undergo evaluation for CAD every 12 months if they have associated diabetes mellitus, known CAD and history of percutaneous coronary revascularization. If however, they do not have DM but otherwise have high risks, they should undergo evaluation for CAD every 24 months. If they have low risk then evaluation for CAD should be done every 36 months.

8. Among acute coronary syndrome patients revascularization should be performed: Emergent PCI is preferred if available. Adjustment of doses for low molecular weight heparin and appropriate IIb-IIIb inhibitors should be made.

9. For coronary artery disease patients they should be treated just like the general population. All cardioprotective medications such as aspirin, beta blockers (carvedilol is preferred), ACE-inhibitors/angiotensin receptor blockers, statins and calcium channel blocker should be used as indicated.

10. All patients on dialysis should be treated as those in the general population with anti-arrhythmic medications; however, dose adjustment must be made for drugs eliminated by the kidneys.

11. Patients who require pacemakers or implantable cardioverter defibrillators should follow the same general guidelines as for the general patient population.

12. All centers providing renal replacement therapies (dialysis) must have an automatic external defibrillator (AED) on standby.

Conclusions

Cardiovascular diseases account for the majority of the deaths among patients with chronic kidney disease and end-stage renal disease. Arrhythmias are the foremost cause of both morbidity and mortality among these patients. Aggressive management of both traditional and non-traditional risk factors for CVD should be adopted. Usage of aspirin, beta blockers, ACE-inhibitors and statins should be encouraged among these high risk patients although the evidence for some of these approaches are still lacking for this patient population. The alarmingly high risks of de novo sudden cardiac arrest and prohibitively high rate of recurrence among those who have survived the first episode should prompt randomized trials examining the role of implantable defibrillators in primary prevention. Prophylactic use of coumadin for prevention of thrombo-embolism among patients with atrial fibrillation should be strongly considered unless a specific contra indication exits. More research is needed to establish the mechanism of cardiac arrest among ESRD patients whether these patients are dying from predominantly tachyarrhythmia such as ventricular tachycardia or ventricular fibrillation or predominantly brady-arrhythmic deaths due to high grade atrio-ventricular block.

References


